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Modified Protamine Zinc Insulin: Comparison with Globin Zinc Insulin and Insulin Mixtures[1]

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SOON AFTER protamine zinc insulin was introduced it became evident that, although a reduction in the number of daily injections was possible in most cases, only patients with mild diabetes could be controlled with one dose per day. Of 350 well-controlled diabetic patients we have treated in the past four years, only 186 (53 per cent) could be regulated with protamine zinc insulin alone, while 164 (47 per cent) required in addition a separate morning injection of regular insulin. Of the 186 patients well regulated with protamine zinc insulin alone, 177 (95 per cent) required 40 units daily or less (average 26 units). Those patients requiring separate morning injections of the two insulins were the more severe diabetics, 148 of the 164 needing over 40 units daily, the average total dose being 55 units. It seems evident, therefore, that some different modification of insulin will prove necessary if we hope to control with one daily injection the majority of moderate and severe cases as well as the mild ones.

Efforts of a number of investigators have been devoted to this problem. The most successful insulin modifications devised have been of two types (table 1): (1) those in which a different protein such as histone or globin is combined with insulin; (2) those in which protamine zinc insulin remains the basic substance but is altered by changing the proportions of added protein and added zinc and by varying the pH. There are three sub-types in this group:

(a) Acid or clear PZI (constant in composition—table 1);

(b) Extemporaneous mixtures—variable in

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pH when regular or crystalline insulin (pH 3) is mixed with PZI (pH 7.2); variable also in content of protamine and zinc if the mixture is varied from patient to patient and also from day to day.

If a standard mixture is used, for example two or three parts of crystalline insulin to one part of PZI, the amounts of the various ingredients may be relatively constant if the mixture is carefully prepared, but the pH is apt to be near 5, the isoelectric point of insulin, at which all of the insulin, crystalline as well as protamine zinc, will be precipitated. This will necessarily greatly alter the time-activity of the insulin.

ing of modified protamine zinc insulin. In addition to our own studies, observations of others treating diabetic patients led us to believe that an insulin with such proportionate effects would be the most widely useful. Joslin (3), for example, found that more than 50 per cent of a series of patients required separate morning injections of PZI and regular insulin, the average doses being 39 units PZI and 13 units regular (proportion exactly 3:1). Assays upon patients (1) and upon rabbits (4) have demonstrated that approximately 75 per cent of the MPZ insulin action is slow (like PZI) and 25 per cent is rapid (like regular insulin).

It is important to emphasize here that MPZ

TABLE 1. CHARACTERISTICS OF INSULINS STUDIED

Insulin	pH	Source of added protein	Solubility	Composition per 100 units	
				Added protein	Zinc
				mg.	mg.
Modified protamine zinc	7.2	Salmon sperm	Turbid	0.625	0.1
Market protamine zinc	7.2	Salmon sperm	Turbid	1.25	0.2
Clear (acid) protamine zinc	3.4	Salmon sperm	Clear	3.8	0.3
Histone zinc	7.0	Thymus	Turbid	3.2	0.2
Globin zinc	3.7	Beef blood	Clear	3.75	0.3
Regular	3.0	None	Clear	None	0.02
Crystalline	3.0	None	Clear	None	0.02

(c) There is also a standard modified protamine zinc insulin, having the same pH as market PZI (7.2) but containing only half the added protamine and zinc (table 1). Approximately 75 per cent of this insulin is in precipitated, slowly absorbed form, while 25 per cent is in solution and is rapidly absorbed.

MODIFIED PROTAMINE ZINC INSULIN

Modified protamine zinc insulin was at first made in our own laboratory but is now supplied for investigative purposes by the Eli Lilly Research Laboratories.[2] The reason for choosing a modification with 75 per cent slow effect and 25 per cent rapid effect was that in our own moderately severe and severe diabetic cases we were using PZI and regular insulin in separate morning injections and in the great majority of cases the proportion giving the best control was PZI, 3 to regular, 1. We have previously reported (1, 2) the steps leading to the design-

[2] Under the designation: Special Modified Protamine Zinc Insulin T-1652 (U40) and T-1716 (U80).

insulin cannot be made extemporaneously by mixing PZI and regular (or crystalline) insulin. Although mixing equal parts of PZI and regular insulin will result in a preparation containing approximately half the protamine and half the zinc in PZI, the pH will be near 5, at which all of the contained insulin is precipitated. Control of the pH by proper buffering is necessary.

COMPARISONS OF MODIFIED PROTAMINE ZINC INSULIN WITH OTHER INSULIN MODIFICATIONS

We have carried out direct comparative studies of MPZ insulin with all of the types of insulins outlined above and listed in table 1. In our first report (1) it was shown that MPZ insulin gives more rapid initial activity than market PZI and that it will control severe as well as mild diabetes with a single injection daily. It was also shown that MPZ insulin will approximately duplicate the 24-hour blood-sugar curve produced by separate morning injections of PZI and regular insulin. Further proof of these points with extension of these

studies and inclusion of a considerably larger number of cases is given in figures 1 and 2.

In our second report (2) clear (acid) protamine zinc insulin and histone zinc insulin were directly compared with MPZ insulin. The modified protamine zinc insulin gave better control than was obtainable with standard protamine zinc insulin, while in 18 patients histone zinc insulin gave poorer control than market PZI. In regulating 11 patients clear protamine zinc insulin was inferior to market PZI.

We wished, therefore, to compare modified protamine zinc insulin with the other two forms of insulin (globulin zinc insulin and insulin mixtures) reported as giving good results in the hands of some investigators. These comparisons are the subject of this paper.

METHOD OF INVESTIGATION

There is no doubt that innumerable forms of insulin can be devised, each of which may be suitable for maintenance therapy in a small percentage of patients. There would be no point in such a procedure, however, since we already have in market protamine zinc insulin a preparation which controls very nicely about

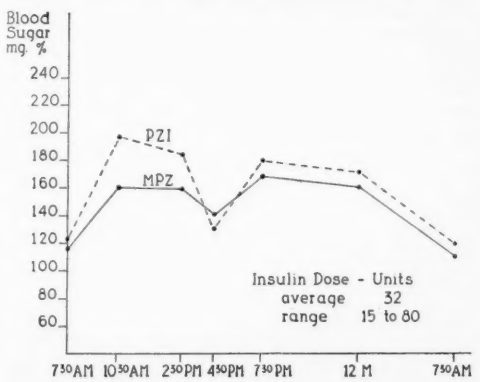

FIG. 1. Composite comparative 24-hour curves with PZI and MPZ insulin on 23 patients. When fasting blood sugar levels are kept approximately normal with PZI, hyperglycemia is apt to occur during the day. If enough PZI is given to control this, hypoglycemia is apt to occur at night. MPZ insulin, however, not only prevents excessive blood-sugar rise after meals, but keeps fasting blood sugar normal and does not tend to provoke hypoglycemia.

half of our diabetic patients (the mild cases). To demonstrate that an insulin modification will be an improvement in the treatment of diabetes, one must show that it will control the majority of moderately severe and severe cases with a single injection daily. If it is necessary to use a separate injection of another form of insulin each morning, the new insulin will offer no advantage, since it is possible to establish good regulation now in nearly all severe un-

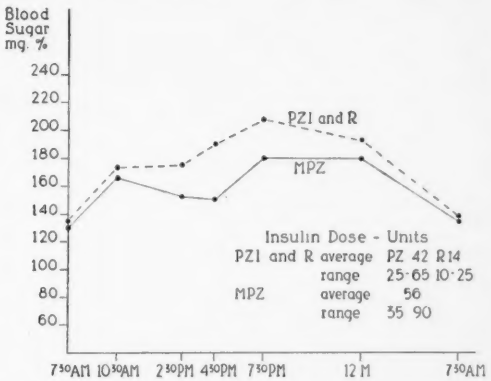

FIG. 2. PZI and regular insulin given in separate morning injections, compared with MPZ. Composite, comparative 24-hour curves on 14 patients. Fairly good control is obtainable with separate daily injections of PZI 45 U and R 15 U, or PZI 60 U and R 20 U, etc. MPZ insulin gives similar but better 24-hour blood-sugar curve with single doses of 60 units or 80 units, etc.

complicated cases with separate morning injections of PZI and regular insulin.

A further point necessary to observe in choosing methods of study is that comparisons of two insulins should be direct, on the same patient, and under controlled conditions of diet, activity, etc.

Therefore, when MPZ insulin and globin zinc insulin are compared in the following studies, or MPZ insulin and an insulin mixture, the comparisons are direct, on the same patient, with the same environment and the same amount of activity. The total dose of insulin is the same and it is given in one injection at the same time, approximately 7:30 a.m., one-half hour before breakfast. All of the studies were made on the Metabolism Ward and the diets were all carefully weighed.

Patients. Diabetic patients were selected for study who were not suffering from any complications which would affect the blood-sugar level. Comparative observations made with the various types of insulin therapy required that each patient remain under observation in the Metabolism Ward for at least several

weeks. Some patients with mild diabetes were included, but a special effort was made to include a large number of patients with more severe grades of the disease since the best test of the various insulin modifications would be on these patients. The patients were partly of the unstable juvenile type and partly of the more stable, middle-aged group. The age range was from 15 to 74 years with an average of 46 years.

Diets. In each case the diet used was that thought to be best for the individual patient, according to his age, size, nutritional status, activity and total caloric requirement. Protein allowances ranged from 56 to 110 gm., fat from 30 to 150 gm. and carbohydrate from 120 to 250 gm. The average carbohydrate allowance was 150 gm. The carbohydrate distribution usually used permitted a night feeding at 9:30 or 10 p.m., containing 20 per cent of the total, with the remaining 80 per cent equally divided among the three main meals. This has been adopted for most of our patients for two reasons: (1) they like it; and (2) spreading the carbohydrate out widely permits smoother control than if a few very large carbohydrate meals are given, no matter what type of insulin is used.

For certain purposes in some of the comparative insulin studies other distributions of the total carbohydrate were employed. These distributions were: 1) only 20 per cent of the carbohydrate at breakfast, with 40 per cent at lunch and at supper, to see whether this would give better results with globin zinc insulin than the usual distribution described above; 2) carbohydrate equally divided among the three meals. The latter plan was tried to see whether it would improve the results obtained with the 2:1 crystalline-PZI mixture and also to determine whether or not the use of a night feeding is necessary with MPZ insulin.

Blood and Urine Sugar Measurements. Each patient was as carefully regulated as possible with one type of insulin, using a single injection before breakfast daily. Sometimes the regulation was started with MPZ insulin; at others, with globin zinc insulin or one of the mixtures. Careful quantitative urine-sugar measurements were made of all urine passed by the patient throughout the period of study, collections being separated into four periods daily: 7 to 11 a.m., 11 a.m. to 4 p.m., 4 p.m. to 9 p.m., and 9 p.m. to 7 a.m. Meals were given at 8 a.m., 12 noon and 5 p.m. Glycosuria was eliminated as completely as possible and an effort was made to bring the blood sugar within normal limits. Blood sugar was determined frequently, usually fasting and at 10:30 a.m. (The method used gives "true glucose" values, not total reducing substance in the blood, the normal fasting range being 70 to 100 mg. per cent.) When the patient was approximately aglycosuric and the blood sugars had shown comparatively little fluctuation for at least four to seven days, a 24-hour blood-sugar curve was determined. Blood for glucose determination was drawn at 7:30 a.m. (fasting), 10:30 a.m., 2:30 p.m., 4:30 p.m., 7:30 p.m., 12 midnight and again at 7:30 a.m. (fasting). All of these blood-sugar values except those taken fasting and those at 4:30 p.m. represent the level two and one-half hours after the preceding meal. The constancy of these intervals lends additional meaning and importance to 24-hour curves constructed from such determinations.

When all criteria had been met and we were satisfied from the previous blood- and urine-sugar determinations, as well as from the 24-hour curve that the best possible regulation had been secured with one form of insulin, the study was repeated using the same total dose daily of one of the other forms of insulin.

Insulin: Modified protamine zinc insulin has already been described and its composition is given in table 1. Globin zinc insulin used was of the usual type (now obtainable on the market).[3] Its composition is given in table 1.

Mixtures of crystalline insulin with protamine zinc insulin in various proportions have been employed. Like Hildebrand and Rynearson (5) we have found that it is possible to control some patients with mixtures containing five parts CI to one part PZI, while others do best with proportions of four, or three, or two, or one CI to one PZI. However, our purpose is not to devise a separate "tailor-made" mixture for each patient but to find whether there is one insulin modification or mixture which will give good regulation in most patients. Fairly good results were obtained in some cases with the

[3] Most of the globin zinc insulin was supplied by the Burroughs-Welcome Company. Some was furnished by the Eli Lilly Laboratories. No difference was noted in the globin zinc insulin from the two sources.

3:2 proportion suggested by Ulrich (6). More promising, however, since it gave better results in a larger number of our cases, and since good results were reported with it by Colwell and Izzo (7), was the 2:1 crystalline-PZI mixture. Since this preparation is evidently the best of the extemporaneous mixtures for general use, comparative curves with it are included in this study.

TABLE 2. COMPARISON OF MODIFIED PROTAMINE ZINC INSULIN WITH GLOBIN ZINC INSULIN

Case	Insulin	Units	7:30	10:30	2:30	4:30	7:30	12	7:30
1	**MPZ**	**15**	**121**	**145**	**132**	**110**	**121**	**118**	**124**
	GZ	15	127	153	112	90	105	130	137
2	**MPZ**	**15**	**84**	**147**	**125**	**144**	**160**	**112**	**90**
	GZ	15	130	182	136	107	121	144	141
3	**MPZ**	**20**	**120**	**190**	**116**	**98**	**124**	**122**	**118**
	GZ	20	138	236	180	56	179	168	145
4	**MPZ**	**30**	**129**	**212**	**131**	**110**	**148**	**136**	**140**
	GZ	30	157	224	120	79	130	144	165
5	**MPZ**	**30**	**101**	**136**	**120**	**149**	**98**	**84**	**90**
	GZ	30	160	213	84	74	135	147	156
6	**MPZ**	**40**	**92**	**135**	**156**	**110**	**95**	**85**	**94**
	GZ	40	158	254	195	69	130	137	175
7	**MPZ**	**40**	**75**	**130**	**124**	**136**	**149**	**133**	**89**
	GZ	40	122	273	145	54	68	125	140
8	**MPZ**	**40**	**157**	**194**	**172**	**159**	**142**	**154**	**149**
	GZ	40	139	233	120	48	75	127	157
9	**MPZ**	**45**	**98**	**134**	**163**	**124**	**115**	**109**	**104**
	GZ	45	144	184	132	64	190	135	148
10	**MPZ**	**45**	**74**	**118**	**96**	**136**	**145**	**124**	**70**
	GZ	45	159	239	108	122	149	130	148
11	**MPZ**	**50**	**165**	**182**	**154**	**160**	**173**	**160**	**154**
	GZ	50	204	261	202	120	113	165	194
12	**MPZ**	**50**	**143**	**120**	**169**	**158**	**188**	**162**	**132**
	GZ	50	199	270	95	41	80	178	190
13	**MPZ**	**65**	**140**	**151**	**120**	**111**	**126**	**143**	**138**
	GZ	65	152	164	72	54	135	131	158
14	**MPZ**	**70**	**146**	**120**	**175**	**160**	**185**	**153**	**126**
	GZ	70	136	260	68	48	110	115	130
15	**MPZ**	**85**	**139**	**121**	**145**	**137**	**190**	**152**	**133**
	GZ	85	128	238	91	52	60	104	122
16	**MPZ**	**90**	**95**	**98**	**112**	**120**	**139**	**124**	**80**
	GZ	90	140	292	54	40	71	147	156
AVERAGE	**MPZ**	**45.6**	**117**	**146**	**138**	**133**	**144**	**130**	**114**
	GZ	45.6	150	230	119	70	116	139	154

RESULTS

Globin zinc insulin compared with modified protamine zinc insulin

(A) With *usual diets*—in direct comparisons upon sixteen patients—MPZ insulin gave better control in thirteen cases (table 2). Equally good control was established in three mild cases with the globin zinc insulin (*Cases 1, 2, 4*). These three patients received 15 units, 15 units, and 30 units respectively and presumably would have been equally well regulated with market protamine zinc insulin. In no case did globin zinc insulin give better control than MPZ insulin. In 8 of the 16 cases the insulin requirement ranged from 45 to 90 units. The average for all patients was 46 units. Each patient in this group received 20 per cent of the carbohydrate in the night feeding.

While receiving globin zinc insulin, 12 of the 16 cases had considerable hyperglycemia and

glycosuria after breakfast (*Cases 3, 4, 5, 6, 7, 8, 10, 11, 12, 14, 15,* and *16*) while in only 2 of the 16 cases did significant hyperglycemia occur at this time with MPZ insulin (*Cases 4* and *8*). The average blood-glucose rise from 7:30 a.m. to 10:30 a.m. with globin zinc insulin was 80 mg. per cent, while with modified protamine zinc insulin it was 29 mg. per cent.

The fasting blood sugar was lower in 13 of the 16 patients while receiving MPZ insulin.

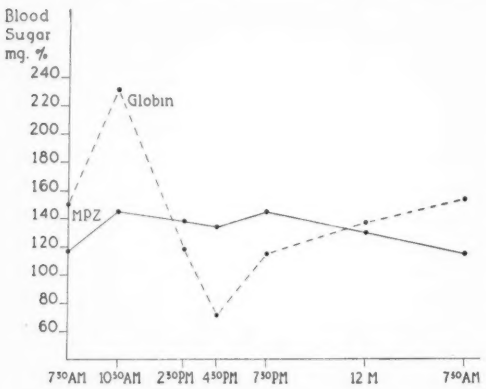

FIG. 3. Composite curves from 16 comparative 24-hour curves with MPZ insulin and globin zinc insulin. Fasting blood-sugar levels are too high with the globin zinc insulin; the after-breakfast rise is not prevented any better than with market protamine zinc insulin (compare with fig. 1) and there is a marked tendency to hypoglycemia in mid-afternoon. MPZ insulin gives smooth control throughout the 24 hours.

In the 4 severe cases having permissible fasting blood-sugar levels (122 mg. per cent to 158 mg. per cent) with globin zinc insulin, there was, however, severe afternoon hypoglycemia (*Cases 13, 14, 15, 16*). In general, the fasting blood sugars with globin zinc insulin were high, averaging 33 mg. per cent higher than with MPZ. We, therefore, agree with others who have found that the globin zinc insulin effect does not last for 24 hours except with large doses.

The outstanding defect in the control with globin zinc insulin was the frequent production of afternoon hypoglycemia. This occurred in 9 of the 16 cases at 4:30 p.m., the blood sugars ranging from 40 to 64 mg. per cent. Hypoglycemia did not occur in any of the patients receiving MPZ insulin. The average blood-sugar fall between 10:30 a.m. and 4:30 p.m. was 160 mg. per cent with globin zinc insulin but was only 13 mg. per cent with MPZ insulin.

Statistical analysis by Student and Fisher's formula shows that the probability favoring MPZ insulin over globin zinc insulin in these 16 case studies is 0.972, showing that the superiority exhibited by MPZ insulin cannot be a matter of chance. It is, therefore, permissible to compare them by composite curves, constructed from average figures obtained in the sixteen cases (fig. 3).

(B) With *special diets.* All of the workers (8) with globin zinc insulin have found this tendency to afternoon hypoglycemia when attempts are made to give doses large enough to control the hyperglycemia occurring after breakfast and to bring the fasting blood sugar within desirable limits. To obviate these difficulties it has been suggested that only 20 per cent of the carbohydrate be given at breakfast (to reduce the after-breakfast rise), 40 per cent at lunch, 10 or 15 per cent in a feeding at 3 p.m. and 40 per cent at supper. It is obvious that this is a distorted diet. A patient who received 40 per cent of his carbohydrate at lunch and 15 per cent at 3 p.m. would ingest 55 per cent of the total 24-hour allowance within 3 hours. It is certainly illogical to do this with patients who have diabetes mellitus, in whom we are endeavoring to lower and stabilize blood-glucose levels.

To study further, however, the properties of globin zinc insulin, we obtained 24-hour blood-sugar curves on four patients receiving carbohydrate distributed as 20 per cent at breakfast and 40 per cent at lunch and at supper. We did not give mid-afternoon feedings in any of our studies, for three reasons: (1) we consider such a distribution of the carbohydrate illogical; (2) patients do not want to eat so soon again after lunch, or so shortly before supper; (3) employed persons and school children cannot stop their occupations in mid-afternoon and take time out for a second lunch period every day.

The four curves with the special diet distribution are shown in figure 4. In three of the four cases, the fasting blood sugars were within permissible limits (106 to 152 mg. per cent). This was the result of our deliberate efforts to give enough of the globin zinc insulin to prevent the excessive blood-glucose rise tending to occur after midnight and to control after-breakfast hyperglycemia. The latter effect was

not obtained, however, since in two of the four cases an extreme blood-sugar rise was observed at 10:30 a.m., in spite of the fact that the four patients in this group received only 20 per cent of their carbohydrate at breakfast. In three of the four patients hypoglycemia occurred (in *Case 1* at midnight; *Case 3* at midnight, *Case 4* at 4:30 p.m.).

The same four patients were given MPZ insulin in the same doses and the same diets to stabilize patients with the mixture, whether it was prepared in the syringe just before injection or in the vial. Fasting blood sugars were consistently higher with the 2:1 mixture. The average fasting blood glucose was 109 mg. with MPZ insulin, while it was 144 mg. with the 2:1 mixture. In 17 instances out of 20 the fasting blood sugar was lower with MPZ insulin. The rise after breakfast was less well controlled in every instance after the mixture than with

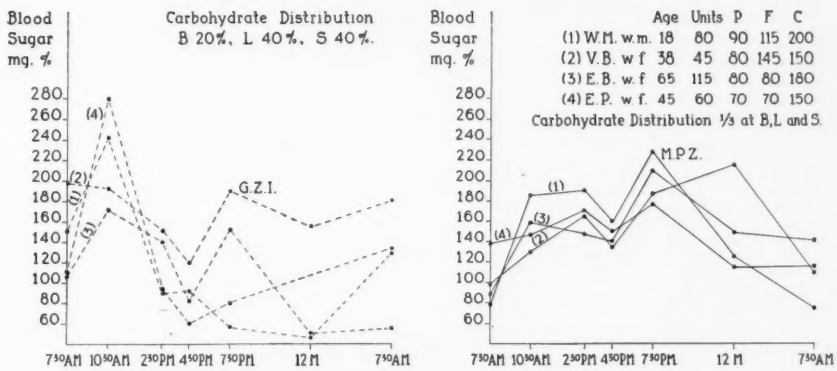
Blood Sugar mg. %
Carbohydrate Distribution
B 20%, L 40%, S 40%.
G.Z.I.
7³⁰AM 10³⁰AM 2³⁰PM 4³⁰PM 7³⁰PM 12 M 7³⁰AM
Age Units P F C
(1) W.M. w.m. 18 80 90 115 200
(2) V.B. w f 38 45 80 145 150
(3) E.B. w f 65 115 80 80 180
(4) E.P. w f. 45 60 70 70 150
Carbohydrate Distribution ⅓ at B,L and S.
M.P.Z.

FIG. 4. Four case studies comparing MPZ insulin and globin zinc insulin when smaller breakfasts and larger lunches were given (no night feeding).

On the left are shown the curves with globin zinc insulin; on the right, the curves on the same patients obtained with MPZ insulin. Globin zinc insulin failed to prevent the after-breakfast rise and tended to cause afternoon hypoglycemia even with the special diet distribution. MPZ insulin gave relatively good regulation throughout the 24 hours, so that a night feeding is not necessary even with these large insulin doses.

were given, with the carbohydrate distributed, however, as one-third at breakfast, lunch and supper. No night feeding was given, to determine whether with patients receiving large doses of MPZ insulin (45, 60, 80 and 115 units, respectively), extra night carbohydrate would prove necessary. No hypoglycemia occurred and relatively good control was obtained. Only three out of the 28 blood-glucose determinations performed in the four 24-hour blood-sugar curves were over 200 mg. per cent and in no case did the glycosuria exceed 10 gm. in the 24 hours.

Mixture of crystalline with protamine zinc insulin (2:1) compared with modified protamine zinc insulin. Ten direct comparisons were performed. The blood-glucose values obtained in the 24-hour curves are given in table 3. Modified protamine zinc insulin gave better control in each of the ten cases. It was difficult

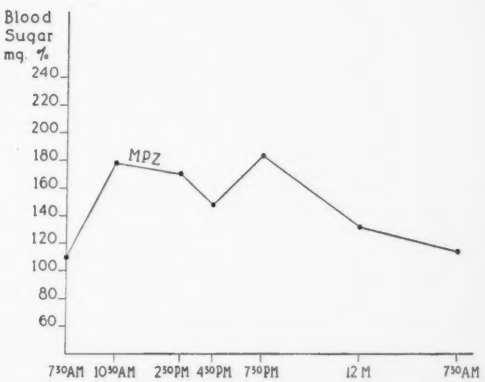

FIG. 5. Composite curve from 10 twenty-four hour curves with MPZ insulin. All patients in this group received carbohydrate equally divided between the 3 usual meals. All patients were severe diabetics, controlled with one injection daily. Insulin requirements were from 40 to 115 units daily (see table 3). Good regulation was possible without night feeding. Smoother, more flat curves, however, were obtained with night feedings (compare with fig. 3).

MPZ insulin. The average rise from 7:30 to 10:30 a.m. with the mixture was 94 mg. per cent, while with MPZ insulin it was 67 mg. per cent. Hypoglycemia at 4:30 p.m. occurred in three of the ten patients receiving the mixture. Because of this tendency to provoke excessive lowering of the blood glucose, Colwell (7) advises the use of a mid-afternoon lunch. For the reasons previously given we did not give a mid-afternoon feeding. All patients in this group received one-third of the carbohydrate at breakfast, lunch and supper. A composite curve of the results of the ten 24-hour blood-sugar curves with MPZ insulin is shown in figure 5. No comparative composite curve could be constructed for the 2:1 mixture because of the irregular results, which failed to show a characteristic curve and did not permit statistical analysis.

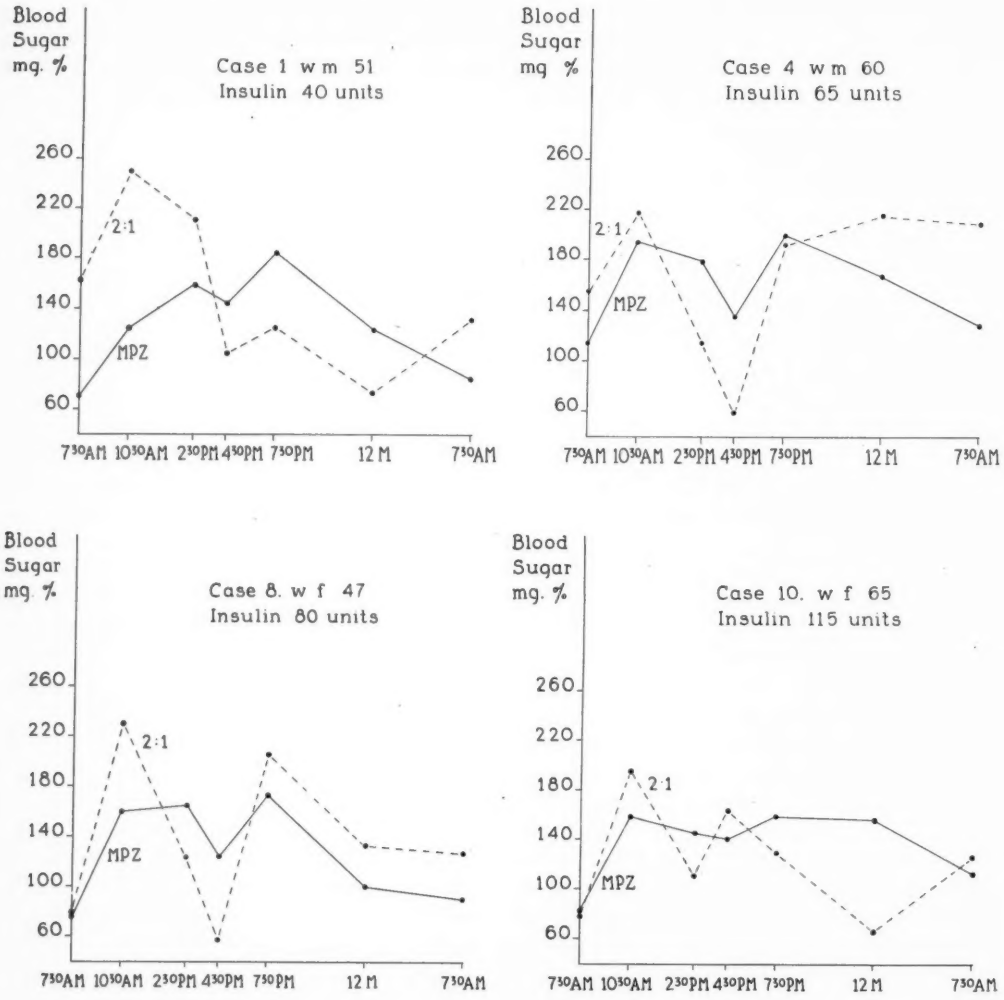

FIG. 6. Comparisons of MPZ insulin and 2:1 mixture. Note better regulation with MPZ insulin. Fasting blood sugars are too high with the mixture, the after-breakfast rise is not prevented, and there is a definite tendency to hypoglycemia at mid-afternoon or midnight.

For comparison, however, four of the individual case studies are illustrated in figure 6. The irregular results obtained with the mixture are

shown in figure 7, in which 48-hour curves are compared. The first and second 24-hour curves obtained with MPZ insulin are quite similar, but the two 24-hour curves obtained with the mixture are very different. Variation of this type was found in comparative 48-hour blood-sugar curves in each of four cases.

DISCUSSION

Fairly good results were obtained with globin zinc insulin in some of the milder cases requiring less than 40 units per day. However, market protamine zinc insulin will also give good regulation in such cases. When compared on moderate and severe cases of diabetes, globin zinc insulin gave relatively poor regulation, even when a special diet distribution was used. Modified protamine zinc insulin gave good regulation with either type diet, with or without a night feeding.

The 2:1 crystalline-PZI mixture gave fairly good control in some cases, but in general gave irregular results, permitting excessive increase in the blood glucose after breakfast and tending to cause hypoglycemia in mid-afternoon or at night. Modified protamine zinc insulin when given in the same doses, even as large as 115 units in a single injection, prevented in most cases the excessive after-breakfast rise and did not tend to cause hypoglycemia.

The only type of insulin therapy giving possibly as good control as that established with MPZ insulin was obtained with separate morning injections of PZI and regular insulin (fig. 2). It seems that with the more normal type diets now usually employed in treating diabetes, a proportion of three parts slow-insulin-action to one part rapid-insulin-action fits the requirements of the great majority of patients. MPZ insulin supplies this desirable proportion of activity in a standard, apparently stable form which can be taken in a single injection daily, obviating the necessity for two separate injections. In 110 case studies we have made over a four-year period, MPZ insulin gave good control in 98 patients (90 per cent). The other 12 patients were so unstable that the insulin dose had to be varied from day to day, preventing good regulation with a single injection daily of any insulin with overlapping effects such as PZI or MPZ.

Market PZI controls mild diabetics with a single daily injection but MPZ insulin improves somewhat the regulation in this group needing less than 40 units per day. Of the 98 patients well controlled with MPZ insulin, 63 (64 per cent) required over 40 units daily, some as high as 120 units (average 73 units). MPZ insulin, therefore, established good control in severe diabetes also.

Globin zinc insulin and the 2:1 crystalline-PZI mixture failed to give any comparable results (table 2, fig. 3, 4; table 3, fig. 6, 7).

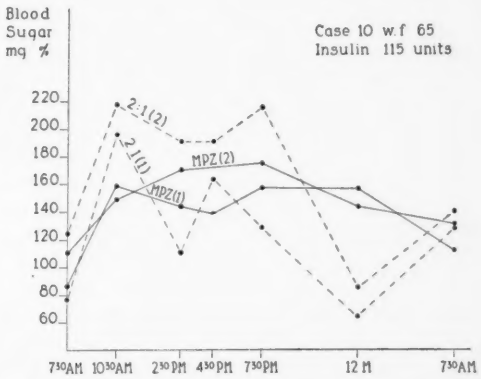

FIG. 7. Comparative 48-hour curves with MPZ insulin and 2:1 mixture. First and second 24-hour curves with MPZ insulin show good control and are almost duplicates. First and second 24-hour curves with 2:1 mixture are very unlike, except that both show failure to control the after-breakfast rise and in both there is a definite tendency to hypoglycemia at midnight.

A natural question presents itself: will it ever be possible to control the majority of diabetic patients with a single injection daily of any one type of insulin? Perhaps diabetic patients differ so widely among themselves and individual patients fluctuate so greatly from day to day that no such standard control will prove possible. Such is apparently the experience of Wilder (9), Peck (10), Sparks and John (11), and Hildebrand and Rynearson (5), who favor using extemporaneous mixtures, "tailor-made," and varying from patient to patient and sometimes varying from day to day.

This is not our experience. We find that practically all mild diabetic patients are well controlled with MPZ insulin and nearly all of our severe diabetic patients can also be regulated with it. We, therefore, see no need for

further use of extemporaneous mixtures, which are variable in effect and confusing to both patient and physician. If one insulin, such as modified protamine zinc insulin establishes good control in 90 per cent or over of all patients, surely there is no need for devising individual extemporaneous insulin mixtures.

Table 3. Comparison of MPZ insulin with 2:1 mixture

Case	Insulin	Units	7:30	10:30	2:30	4:30	7:30	12	7:30
1	**MPZ**	**40**	**70**	**124**	**159**	**142**	**181**	**122**	**82**
	2:1	40	162	250	210	103	124	71	130
2	**MPZ**	**45**	**99**	**153**	**176**	**164**	**198**	**135**	**108**
	2:1	45	140	232	110	60	98	180	126
3	**MPZ**	**60**	**135**	**205**	**170**	**158**	**200**	**122**	**115**
	2:1	60	155	231	196	178	193	95	119
4	**MPZ**	**65**	**114**	**194**	**178**	**134**	**199**	**166**	**128**
	2:1	65	155	217	114	58	192	214	208
5	**MPZ**	**65**	**135**	**184**	**160**	**142**	**163**	**133**	**125**
	2:1	65	148	237	250	163	246	180	110
6	**MPZ**	**75**	**158**	**200**	**172**	**140**	**180**	**154**	**145**
	2:1	75	145	251	212	185	233	158	167
7	**MPZ**	**80**	**78**	**184**	**190**	**158**	**204**	**110**	**82**
	2:1	80	229	270	205	170	175	202	135
8	**MPZ**	**80**	**77**	**159**	**163**	**123**	**172**	**100**	**90**
	2:1	80	79	230	122	57	195	132	126
9	**MPZ**	**100**	**142**	**195**	**181**	**166**	**168**	**126**	**149**
	2:1	100	149	264	146	92	196	157	174
10	**MPZ**	**115**	**82**	**158**	**144**	**140**	**158**	**156**	**112**
	2:1	115	78	195	110	162	128	64	124

SUMMARY

In 16 direct comparative case studies, modified protamine zinc insulin gave better control in 13 patients than globin zinc insulin, while only three diabetic patients were equally well controlled. In no case did globin zinc insulin establish better regulation than modified protamine zinc insulin. Globin zinc insulin failed to prevent after-breakfast hyperglycemia in 12 of the 16 cases and caused afternoon hypoglycemia in nine of the 16. Fasting blood sugars were higher in 13 of the 16 cases when globin zinc insulin was used.

Even when special diets were employed, allowing a smaller breakfast and a larger lunch, the same defects in control were observed with globin zinc insulin. A mid-afternoon feeding was not given in any of these studies because it was considered illogical and impractical.

In 10 direct comparative studies with an extemporaneous mixture made with two parts of crystalline insulin and one part of protamine zinc insulin, modified protamine zinc insulin gave better control in every one of the 10 cases. Irregular results were obtained with the mixture, with failure to duplicate 24-hour curves. In general the rise in blood sugar after breakfast was poorly controlled with the mixture and there was a tendency to hypoglycemia at mid-afternoon or midnight.

In a total of 110 case studies conducted over a four-year period, good regulation was established in 98 patients (90 per cent) with a single injection of MPZ insulin daily. Severe as well as mild cases were well controlled, 64 per cent of the well regulated cases requiring over 40 units daily, some as high as 120 units (average 73 units).

CONCLUSIONS

(1) The use of multiple forms of insulin should be discouraged. Good therapy of diabetes requires simplicity. Globin zinc insulin

does not satisfy the requirements for an insulin of intermediate activity and its introduction on the market has unfortunately added to the confusion in this field.

(2) The use of variable extemporaneous mixtures, perhaps a necessary step in furthering our knowledge, has also added to the confusion. Since 90 per cent of a series of 110 diabetic patients were well regulated with modified protamine zinc insulin, there seems to be no necessity for prescription of individual insulin mixtures.

(3) The 2:1 crystalline-PZI mixture failed to give a good, predictable, intermediate type of response.

(4) Two forms of insulin should be sufficient: a) modified protamine zinc insulin such as that used in these studies which might well be substituted on the market for standard protamine zinc insulin, since it will control a very much larger percentage of patients with uncomplicated diabetes; and b) regular (or crystalline) insulin for use in diabetic emergencies and whenever supplementary insulin is required.

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A Case of Cushing's Syndrome Treated with Testosterone Propionate[1]

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CUSHING'S syndrome occurs rather infrequently in children. Of the cases reported, as reviewed by Farber, Gustina and Postoloff (1), only ten were those of boys, and in three the diagnoses were questionable. Medical management of these cases up to recent years has been very unsatisfactory. Albright and his colleagues (2) in 1940 presented their hypothesis on the use of testosterone propionate in the management of Cushing's syndrome. This was based on the ability of the androgen to maintain the patient in a positive nitrogen balance by stimulating tissue synthesis. All of the patients treated at their clinic, however, were females. So far as can be determined there have been no cases reported in the young adult male in which testosterone propionate has been used.

CASE REPORT

This case is that of a white boy, P. P., age 17, admitted to the Charles S. Wilson Memorial Hospital on January 7, 1944 complaining of severe pain in the back, of three months' duration, which came on suddenly while he was lifting a case of beer. The pain had become progressively worse in the lower dorsal and lumbar spine. He gave a history of gaining excessive weight for the preceding two years, the amount of which was undetermined. His weight at the time of admission was 163 pounds; height, 66 inches. He gave a history of normal growth and mental development; previous illnesses were not remarkable except for rheumatic fever in 1940, for which he was hospitalized three months. There were no residual valvular defects. For two months the patient had noted a decrease in nocturnal emissions. An x-ray plate of the chest, taken in 1943, ruled out fracture.

Physical examination at the time of admission revealed an alert, markedly obese, white boy, with generalized muscular weakness; the obesity was confined to the face, neck and trunk; the belly protruded markedly. The face had a typical porcine expression. It was hairy, had numerous acnic papules and was florid with several areas of telangiectases. In the axillae and over the lower abdomen there were many purple striae (see accompanying figure). The eyeground and visual fields were normal. Nose, mouth and throat were normal. The heart and lungs were normal. Blood pressure on admission was 180/120. The liver, kidneys and spleen were not palpable. Both extremities were thin. The reflexes were normal. Forward or side movements of the body elicited pain over the lumbar vertebrae; walking also was painful and difficult. The genitalia were normal with a male type of hair distribution. The hair on the rest of the body was increased with marked hirsutism of the back.

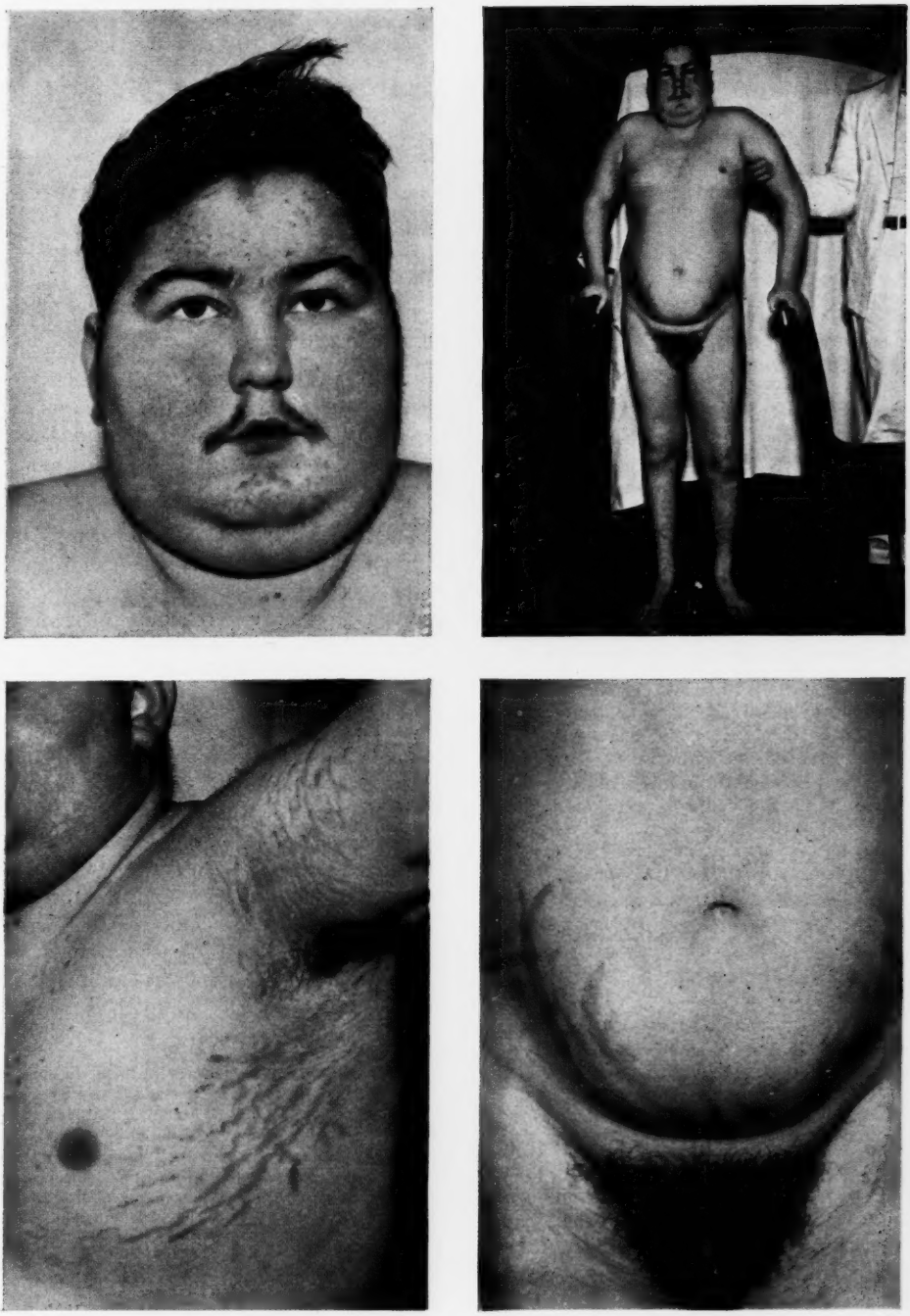
X-ray findings on admission showed striking osteoporosis of the spine and of the ribs which was not present on examination of the ribs on June 2, 1943. There were no other pathological changes of the bony structures of the dorsal and lumbar spine. A flat picture of the kidneys showed no abnormal mass visible in the area. An intravenous pyelogram revealed no displacement of the kidneys. The skiagram of the skull showed a normal bony structure including a normal sella turcica.

Prior to testosterone propionate therapy, laboratory findings were as follows: the urine contained no albumin or sugar; the red blood-cell count was 4,570,000; the hemoglobin, 14 gm.; the color index, 1.0. The leucocyte count was 8,900: neutrophiles, 77%; lymphocytes, 23%; monocytes, 0; eosinophiles, 0; and basophiles, 0. (See table 1 for the remainder of the data). Alkaline phosphatase was found to be 3.9 units per 100 cc. of serum. Blood-serum cholesterol was 150 mg. per 100 cc. The results of the glucose-tolerance test are given in table 2. One hundred grams of aminoacetic acid was given and blood-sugar values determined as in a glucose-tolerance test; the results are shown in table 2. The total 17-kerosteroids were 12

TABLE 1

Test	Before Treatment	During Treatment
Blood creatinine	1.2 and 1.1	1.5
Urine creatinine	0.9 and 1.08	1.16; 1.3 and 1.4
Blood creatine	3.2	4 and 6.6
Urine creatine	0	0.17 and 0.254
Blood calcium	11.7	0 No determination
Urine calcium	0.25	0.24

[1] Read before the Twenty-Seventh Annual Meeting of the Association for the Study of Internal Secretions, Chicago, Illinois, June 13, 1944.



Illustrations of the patient demonstrating typical skin changes in Cushing's syndrome.

mg., of which 4 mg. were beta-alcoholic. Serum sodium was 148 milli-equivalents per liter.

The patient was put on a regular diet. His general condition during the next three weeks became progressively worse so that he was bedridden and could not sit up; even turning over in bed was difficult. He was started on testosterone propionate on January 29, being given 25 mg. intramuscularly three times a week. On February 8 he was able to get out of bed, although only with difficulty. His condition gradually improved so that he was capable of sitting up in a chair. The testosterone propionate was then discontinued. Three days later he suffered a relapse. Medication was resumed at the same dosage and the patient again showed a marked improvement in strength and ability to move about. On May 15 he was out of bed and walking for the first time in ten weeks with only slight pain in the lumbar region. He was fairly comfortable for the next two weeks after which the pain in his back again became severe. X-ray examination showed no change in the osteoporosis since January but there was a slight wedge formation which was most pronounced in the 11th and 12th dorsal and first lumbar vertebrae. The 12th dorsal vertebra particularly showed a marked decrease in height. Since May 16 the patient has been receiving 25 mg. of testosterone propionate a day and has shown a marked subjective improvement. He stated that he felt "peppy" after the injection.

The patient's weight has increased so that he now (June, 1944) weighs 171 pounds. During the period of treatment the patient experienced 5 nocturnal emissions a month. His blood pressure has remained fairly constant, the systolic fluctuating between 168 and 191, the dystolic between 110 and 125. There has been practically no change in the acne on his face since treatment was instituted.

For laboratory findings during testosterone propionate therapy see tables 1 and 2.

TABLE 2. GLUCOSE AND AMINO-ACID TOLERANCE TESTS

	Before Treatment		During Treatment	
	Blood sugar (mg. %)	Blood sugar (mg. %) after 100 grams of amino-acetic acid	Blood Sugar (mg. %)	
			Test 1	Test 2
Fasting	74	104	100	78
1 hour	159	130	194	175
2 hours	172	126	171	165
3 hours	168	130	100	135

DISCUSSION

This boy presents the clinical picture of Cushing's syndrome. It will be noted, however, that two of the minor features are not present, namely, the mild erythrocytosis and impotence. Under testosterone-propionate therapy there has been no improvement in the osteoporosis or in the blood pressure. There was a slight increase in the excretion of creatinine. The blood level as well as the excretion of creatine were markedly increased. There was no increase in the excretion of calcium. The glucose tolerance has never returned to normal. There has been an increase in weight of 8 pounds during testosterone propionate therapy, with marked increase in muscular strength. It will be noted that on one experiment in which pure amino acid was used in place of glucose there was no interference in the break-down of the amino acid into glucose. Although the patient is not able to walk about normally at the present it is felt that this is partially due to the wedging of his lower vertebrae. This can probably be corrected by orthopedic appliances.

SUMMARY

The case is presented of a boy, age 17, showing typical signs of Cushing's syndrome: osteoporosis of the spine and ribs, diabetic glucose tolerance curve—resistant to insulin, hypertension, decrease in libido, hirsutism, generalized muscular weakness, buffalo type of fat distribution and purple striae with normal genitalia. The urinary 17-ketosteroids were normal. The serum sodium was markedly elevated. X-ray plates of the sella turcica and adrenal regions showed normal conditions. Under testosterone propionate treatment the boy showed marked gain in strength with a very pronounced increase in the excretion of creatine and a slight increase in creatinine excretion. The blood creatine was also increased. There was an increase in libido. There was no change in the osteoporosis, hypertention or calcium excretion.

I am indebted to Dr. Edward Jones of the Charles S. Wilson Memorial Hospital for referring this case to me. I wish to thank Dr. Nathan B. Talbot of the Massachusetts General Hospital for the 17-ketosteroid determinations and Dr. A. M. Butler of the same institution for assay of the serum-sodium values. Part of the testosterone propionate used was supplied through the courtesy of Dr. E. Oppenheimer of the Ciba Pharmaceutical Company. The color plates were supplied through the courtesy of Ansco, Binghamton, New York.

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Parathyropituitary Syndrome in Pituitary Eosinophilism[1]

ROBERT M. PERLMAN, M.D.[2]

THE SIMULTANEOUS occurrence of pituitary disorders and irregularities in calcium metabolism resulting from hyperparathyroidism is frequent enough to warrant close scrutiny and analysis. In an earlier paper (1), abnormal parathyropituitary symptom-complexes were visualized in two categories:

A) Hyperparathyroidism coincidental with eosinophilic hyperpituitarism; and

B) Hyperparathyroidism in hyperpituitarism of the basophil variety.[3]

Consideration of the first category will be undertaken here.

THE PARATHYROPITUITARY SYNDROME AS IT MAY APPEAR IN ACROMEGALY

Erdheim, 1903 (2), reported a case of acromegaly in a 42-year-old male whose pituitary body was greatly enlarged and presented a microscopic picture of adenomatous growth. In addition to the pituitary adenoma, the same case presented eccentric hypertrophy of the left ventricle with aortic valvular insufficiency, stasis of the organs, plus a form of polyglandular syndrome which included a struma colloides diffusa, an extensive pancreatic necrosis, and *three parathyroid bodies of unusual size* (four found and identified). No particular mention was made of the kidneys.

The case of Josefson, 1915 (3), another example which will serve to illustrate the parathyropituitary syndrome in acromegaly, was summarized by Cushing and Davidoff, 1927 (4). Their complete version follows:

> . . . An acromegalic youth, aged 26, height 191 cm., weight 94.3 kg., showed at autopsy, in addition to a large chromophilic hypophysial adenoma, organs with the following weights: heart 460 gm., liver 3400 gm., kidneys 920 gm., spleen 480 gm., a colloid thyroid 55 gm., thymus 20 gm., pancreas 100 gm., adrenals 40 gm., with adenomatous formations; testes normal.
>
> The parathyroids are thus described: "At the right of the thyroid there is a parathyroid as large as a bean and at the left a rounded tumor-formation larger than a walnut which lies completely separated from the thyroids in a fibrous capsule of its own. It measures 6×4×2.5 cm. A section through this shows a compact rather soft mass. Histologically one of the parathyroids is composed of a number of cell islands resembling adenoma, the structure suggesting an hypophysial adenoma, but here and there are cells which are arranged in palisade fashion as if tubulous. The parathyroid tissue itself (apart from the adenoma) shows on the whole normal conditions though they are perhaps richer in cells than usual."

Schlegel, 1940 (5), claimed that Josefson wrote of an *acromegalic whose skull-bones were thin as paper and easily cut by a knife*. A pronounced hyperplasia of the parathyroid glands led Josefson to the conclusion that *increased parathyroid body activity, resulting from the pituitary adenoma, led to mobilization of the bone calcium*.

The monograph of Cushing and Davidoff, 1927 (4), dealt with the pathological findings in four autopsied cases of acromegaly (table 1) and, for the time at which the study was made, contains a complete discussion of the significance of such findings. It seems that a critical analysis of the data for the four cases permits their probable separation into two chief groups: simple acromegaly (*Cases II* and *IV*) and acromegaly with a much heavier polyglandular participation (*Cases I* and *III*). A *Parathyropituitary Syndrome in Nephritics*, as it may be stated, is involved in the latter and more complicated category of acromegaly. The

[1] The data in this paper were taken from the dissertation submitted by the author in partial fulfillment of the requirements for the degree of Doctor of Medicine (privately printed under the auspices of the Institut d'Anatomie Pathologique, UNIVERSITE DE GENEVE, Imprimerie Franco-Suisse, Ambilly, France, May 1942). Some of the material from this thesis was subsequently published under the authorship of E. Rutishauser (15), with the statement: "Die Arbeit erscheint ausführlich als Diss. Genf von R. M. Perlman(n), 1942." The author wishes to record his grateful appreciation to Prof. Rutishauser for giving him the opportunity to carry out this work.

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[3] A paper dealing with the parathyropituitary syndrome in pituitary basophilism is now being prepared for publication.

TABLE 1. WEIGHTS OF NORMAL AND ACROMEGALIC ORGANS[1]

	Height	Weight	Lungs	Heart	Liver	Kidneys	Spleen	Thyroid	Thymus	Adrenals	Pancreas	Gonads
			gm.	gm.	gm.	gm.	gm.	gm.	gm.	gm.	gm.	gm.
Normal male	172 cm.	70 kg.	920	350	1500	300	200	45	14±	12	80	22
Normale female	155 cm.	55 kg.		250								14
Case I: male aged 52 duration 30 yrs.	185 cm. 6′2″	97 kg. 213 lbs.	2550	1050	3150	853	535	310	(?)	43	225	73
Case II: male aged 40 duration 13 yrs.	198 cm. 6′6″	122.4 kg. 269 lbs.	1930	480	3380	565	385	105	8.2	43	83	23
Case III: male aged 35 duration 20 yrs.	173 cm. 5′8″	100 kg. 220 lbs.	(?)	1000	2480	650	(?)	100	78.0	30	150	(?)
Case IV: female aged 51 duration 21 yrs.	157.5 cm. 5′2″	68 kg. 151 lbs.	(?)	460	2500	695	240	(?)	(?)	18	(?)	13
Largest recorded weights			Osborne 2922	Osborne 1275	Dallemagne 5900	Dallemagne 1170	Lewis 1169	Gedde 312	Case III	Schultze 57	Launois 250	(?)

[1] Taken from Cushing and Davidoff, *loc. cit.*

most significant bases for separation seem to be in the obvious differences between the parathyroid glands, kidneys, heart, and perhaps the pancreatic and adrenal glands in the cases of simple acromegaly (where these organs more closely approximate the normal) as compared to these same organs in cases fitting definitely into the parathyropituitary syndrome.

Summing up, table 2 contrasts the findings in the parathyroid glands, kidneys, pancreas and heart for all four cases. The parathyroid glands, identified in only two (*I* and *III*) of the

TABLE 2. ANATOMO-PATHOLOGICAL FINDINGS OF PARATHYROID GLANDS, PANCREAS, HEART AND KIDNEYS IN CUSHING AND DAVIDOFF'S FOUR CASES OF ACROMEGALY

Case	Parathyroid Glands	Pancreas		Heart		Kidneys			
						Weight			Description
		Weight gm.	Description	Weight gm.	Description	Right gm.	Left gm.	Both gm.	
I	Four found: Largest measured 1×0.8×0.5 cm. Histological structure "suggested proliferative activity."	225	A few small fibrous patches; occasional monuclear cell groups; thickened walls in smaller arteries; Normal isles of Langerhans, small, few.	1050	Extraordinary concentric hypertrophy (left ventricule in particular). Occasional scarred patches with atrophic muscle fibres. Small amount arteriosclerosis.	478 (17.5 ×9.0 ×8.5 cm.)	375 (17.5 ×8.0 ×6.0 cm.)	853	Tubules dilated; glomerules large. Cortical arteriosclerotic scars infiltrate by mononuclear cells with atrophic tubules and hyalinized glomeruli. (Multiple infarcts).
II	None identified	83	Interstitial connective tissue increased; especially, about the ducts. Alveoli and isles of Langerhans essentially normal.	480	Cardiac muscle extremely fragmented in some areas; otherwise, normal. Considerable aortic and blood-vessel thickening with intimal proliferation in places.	285	280	565	Essentially normal.
III	2 upper glands found. Smaller was 0.4 cm. in long diameter; larger was 0.9 cm. in long diameter. Each contained a central adenoma.	150	Small acinar adenoma (1 cm. in diameter). Interlobular fat infiltration. Islets unusually large and possibly increased in number.	1000	Enormous myocardial hypertrophy (especially, in left ventricular wall). All cavities greatly dilated; widened valvular orifices.	310	340	650	Marked passive congestion. Oedema. Swollen cells with glycogen and vacuolization in loops of Henle.
IV	None identified.	(?)	No discernible abnormalities. Zymogen granules abundant in acinar cells. On long search, a single island was found sclerosed.	460	Much epicardial fat. A few patches of atheromatous degeneration in coronary arteries. Subintimal atheromatous areas at aortic base.	300	395	695	Surface yellower than normal. Cortex considerably widened and irregular. Small calculus in right renal pelvis; otherwise, essentially normal.

four cases, showed "proliferative activity" in *Case I* and central adenomas in *Case III*. (In this particular case, an adenomatosis of the other endocrine organs was especially marked.) The kidneys were essentially normal, from the histological viewpoint, in *Cases II* and *IV* and pathologic in *Cases I* and *III*. The pancreas varied immensely in weight and structure in the four cases: it was approximately two and three times the normal size in *Cases I* and *III* respectively, and essentially normal in *II* and *IV*. The heart was enormously enlarged in *Cases I* and *III*, particularly due to left ventricular myocardial hypertrophy, but *Cases II* and *IV* presented no unusual aspects aside from fairly enlarged hearts as they are apt to occur in acromegalics.

The heart and kidneys in *Cases I* and *III* merit special consideration. In the case of a 13-year-old male mongrel dog (6), possessing coincident parathyroid and pituitary (atypical eosinophilic) adenomas, plus involvement of

FIG. 2. Cross-section of heart to show extreme myocardial hypertrophy of left ventricle.

most of the other endocrine glands and von Recklinghausen's bone disease, grave chronic nephritis and an enormously hypertrophied myocardium were present (figs. 1 and 2). It was shown that a more or less vicious cycle prevailed between parathyroids and kidneys: hyperparathyroidism, probably resulting from the pituitary tumor, produced calcium and bone metabolism disorders which affected the kidneys. Disturbed renal function, in turn, intensified the phenomena of hyperparathyroidism. Cushing and Davidoff could not explain the enormous heart volumes in *Cases I* and *III*. A glance at the work of Mason, 1936 (7), reveals that heart failure is not at all uncommon in acromegaly. Of 23 patients afflicted with this disease, 17, or 75 per cent, showed evidence of heart failure and six died from that cause. These six had splanchnomegaly, an enlarged heart and an eosinophilic pituitary adenoma. *Two cases presented enormous hearts which weighed 1140 gm. and 1400 gm. respectively.* The hypertrophy was considered to be due to an increase of work-demand on the heart and probably first occurred to compensate for the patient's growth and to meet the increased demands of the splanchnomegaly often pres-

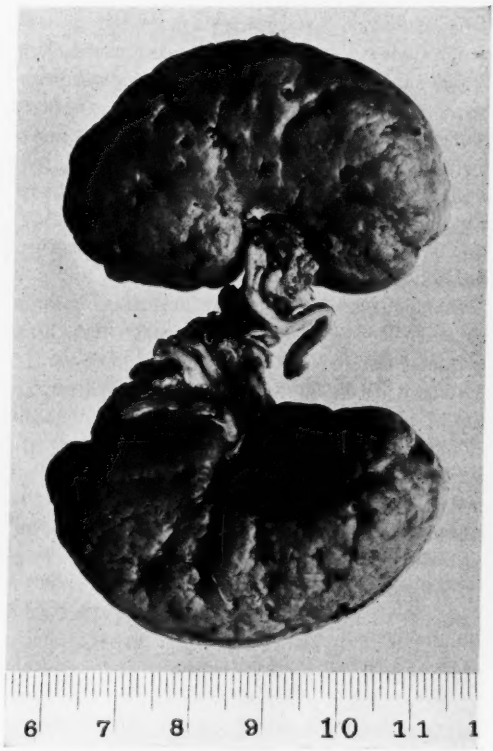

FIG. 1. Nephritic kidneys showing granular surfaces containing multiple cysts.

ent. The hormonal disturbance produced by the adenoma led to general muscular weakness. The heart, being stimulated by hormonal influence to abnormal growth, reached the stage of diminished reserve which it attempted to meet by further hypertrophy.

If one adds to Mason's explanation the common knowledge that certain nephropathies (sub-clinical, chronic or acute) or arterial hypertension—whether of the primary "essential" type or secondary to chronic nephritis—give rise to the condition denominated *concentric hypertrophy* of the left ventricle, a substantial basis is found to explain the enormously enlarged heart found in the case of the nephritic dog (see above) and in the cases described by Erdheim, Cushing and Davidoff (*I* and *III*) and Mason. Growth hormone, increased work-demand, general muscular weakness (calcium-metabolism disorders resulting from parathyroid disequilibrium), stage of diminished reserve and chronic nephritis contribute, all together, to the formation of another vicious cycle which finds one of its issues in extreme myocardial hypertrophy.

Additional reports are found in the literature of cases which embody the parathyropituitary syndrome as it may be manifest in acromegaly. A giant parathyroid tumor observed in what was termed a case with external appearances of frank acromegaly in a 51-year-old male—who died the day after admission to the hospital—was announced by Hadfield and Rogers, 1932 (8). These investigators mentioned that the postmortem examination revealed an enlargement of the pituitary fossa and a softening of the clinoid processes, considerable enlargement of the anterior lobe of the pituitary with capsule incomplete and a small, yellowish pin-head-sized nodule on the upper surface; but they failed to include a histological diagnosis of the pituitary structure. They claimed, nevertheless, that the jaw, hands, tongue and chest rendered external appearances pathognomonic of Pierre-Marie's disease.

Other autopsy findings were: left-sided cardiac hypertrophy with pale, soft myocardium (heart 28.5 ozs. or 807.98 gm.), advanced aortic atheroma, fibrotic induration of spleen, sclerosis of kidneys with slight enlargement, gravel in pelvis of one kidney, diffuse sclerosis of pancreas, and a single greatly enlarged parathyroid gland (measuring $8 \times 4 \times 2.5$ cm.) which the authors considered as "gross adenomatous enlargement of one parathyroid of unknown cause and quite possibly unrelated to the skeletal changes." The thyroid was somewhat enlarged, fleshy, and contained numerous small adenomata.

Hadfield and Rogers stated that the parathyroid tumor was not of recent formation, that the glandular tissue appeared normal and active, but there was not any clinical or radiological evidence of skeletal resorption. One wonders how such evidence might be forthcoming: these same workers informed their readers that their investigations were confined to the postmortem examination. No clinical, histological or radiological report of skeletal structure was included in the discussion. In order to lend any value to the discussion, a statement on skeletal structure must always be based on a histological investigation. This old lesson of experience appears to have been forgotten by certain pathologists as well as clinicians; for example, one of Fischer-Wasel's pupils mentioned a case of parathyroid tumors with calcium metastases in a subject possessing a normal osseous system. No histological examination was made. Actually, it is well known that pronounced bony disturbances, such as heavy fibrous osteopathies as well as certain forms of osteomalacia, may remain unrecognized macroscopically.

Since Pierre Marie, 1886, described the disease entity which today bears his name, classical papers on this subject appear, unfortunately, to be greatly lacking in histological detail of the bony structure in acromegalics. Diagnosis has been made primarily on the basis of roentgenological evidence (enlarged sellae, characteristic tufting of the terminal phalanges), acral enlargements, and eosinophil anterior-lobe pituitary adenomas discovered in specimens taken at biopsy or autopsy. It appears that even Cushing and Davidoff gave wholly inadequate microscopic descriptions of the bones in their four autopsied cases of acromegaly. If this point of view is correct, one can suppose that a more thorough procedure (the same applies to cases of Hadfield and Rogers,

Josefson and others) might result in findings—in *Cases I* and *III*—somewhat analagous but perhaps not quite so pronounced as those reported in the case of the nephritic dog. This supposition is partially confirmed by Junet's histological study of the skeletons in three cases of acromegaly in aged women, 1939 (9). None of the three cases is a definitely outstanding example of the parathyropituitary syndrome. In two cases of pure acromegaly, the author mentions—in addition to the constructive bony processes—*distinct fibrous neoformations and rather heavy osteoclastic phenomena in certain regions;* however, he attached no pathological significance to these occurrences. Nevertheless, he stated: "Naturally, the secondary alteration of the bone in the growing period is a very complex phenomenon into the details of which it is not possible for us to enter (sic!). . . ."

An extremely intriguing clinical presentation was made by Schlegel, 1940 (5). His patient, a 20-year-old housemaid, was depicted as an acromegalic with a pituitary tumor. The acromegaly symptom-complex began when she was 18 years old. At the age of 17 years, however, there was a history of progressively increasing spinal curvature. Other symptoms were amenorrhea, millet-grain and pea-sized pigmented spots strewn over the entire body, scoliosis, kyphoscoliosis and lordosis. Appearing simultaneously with the acromegaly, hyperthyroidism and consequent compression phenomena necessitated a strumectomy several months later. At twenty years of age, roentgen examinations revealed brusque tumoral growth of the pituitary, as translated from a doubly enlarged sella turcica with significant adjacent osseous destruction. Deep roentgenotherapy of the pituitary body, started without complications about six months earlier, was resumed but resulted in a strong and typical attack of tetany. The blood calcium dropped to 8.2 mg. %. The attack was relieved quickly by the intravenous and oral administrations of calcium. Three weeks later, another attempt was made at roentgenotherapy. Before this treatment the serum calcium rose as high as 11.5 mg. per 100 cc. Two days after the third roentgen session, another typical attack of tetany occurred. Further irradiation was considered to be contra-indicated. The serum calcium dropped to 8.5 mg. % and was increased with difficulty to a level of 11.5 mg. % and maintained at the normal level by treatment with calcium, ammonium chloride, and A. T. 10 (Dihydrotachysterol).

Schlegel sought to explain the phenomena of his case in the following manner: a hypoactivity of the parathyroid glands probably resulted from ischemia following ligature of the four arteriae thyreoideae in the course of the patient's thyroidectomy. This led to a reduction to within normal limits of the serum calcium which had been augmented, indirectly, by the parathyroid bodies as a result of and under the pituitary tumor's influence. "Under the circumstances," reasoned Schlegel, "postoperative tetany would have been the consequence if our patient hadn't been afflicted with a pituitary tumor, but presented instead a simple Morbus Basedow. In this manner, the pituitary tumor, which otherwise progresses with significant consecutive hypercalcemia, impeded the occurrence of manifest tetany following stronger stimulation, in this case, of the damaged parathyroid glandules. The hypophysis was, however, checked through roentgenotherapy in its parathyroid gland-influence function to so vast an extent that a renewed blood-calcium drop took place and now led to the declaration of manifest tetany. . . ."

By means of a differential diagnosis, Schlegel eliminated the possibility of post-operative latent tetany and the "Frühreaktion" following brain tumor irradiation. In this fashion, he confirmed his foregoing conception of the mechanism responsible for the clinical picture of his case. He concluded: ". . . therefore, our apprehension that roentgen irradiation of the hypophysis can—indirectly by way of the parathyroid glands and under particular circumstances—lead to manifest tetany is, with the greatest probability, correct."

Gurevic's results (10) would harmonize with Schlegel's conclusions. The former found that the serum calcium fell to 8 mg. % after roentgen irradiation of anterior-lobe pituitary tumors.

DISCUSSION

Eosinophilic hyperpituitarism, usually subclinical, indicates its presence in many ways.

Well-known facts are the following. Pregnancy is often accompanied by physical signs of acromegaly, varying widely in degree. Symptoms which may be attributed to an upset in the finely adjusted balance between hypophysis and ovaries usually disappear with the termination of pregnancy. In pregnancy, the anterior pituitary lobe may hypertrophy to more than double the original size, owing primarily to increased numbers and dimensions of the "Hauptzellen." The gland usually returns to normal when pregnancy is terminated. Williams (11) indicates that disorders of calcium and bone metabolism (osteomalacia, the formation of osteoid tissue, etc.) occur frequently and are associated with the supply of calcium salts to the foetus; in fact, certain authors regard them as physiological in all pregnancies.

The foregoing conditions are not confined to pregnancy alone. One frequently encounters individuals, apparently normal in every other respect, who possess facial or other traits which are either faintly, moderately, or strongly suggestive of acromegaly.

Atkinson (12) showed definitely that the bony affections in acromegaly were not confined solely to overgrowth. In 584 cases of acromegaly the spinal column was normal in only 16.4% and altered in 83.6%. Kyphosis was found in 70%, kyphoscoliosis in 16%, and scoliosis in 8%. Nemenow and Jugenburg, 1928 (13), described significantly augmented (17–18 mg. %) serum calcium in 18 cases of acromegaly (13 females; 5 males). Dibold, 1931 (14), confirmed the observation that a considerable amount of calcemia was found in acromegaly as a result of increased parathyroid activity.

SUMMARY AND CONCLUSIONS

Varying degrees of clinical and sub-clinical pituitary and parathyroid hyperactivity are, no doubt, much more frequent than one might judge from known and manifest tumor cases. According to the available evidence, declared or definite pituitary eosinophilism may find expression in either one of two extreme forms: 1) simple acromegaly; or 2) acromegaly complicated by a polyglandular adenomatous condition of the endocrine series, disproportionate splanchnomegaly affecting chiefly the parathyroids, heart, liver and pancreas; in addition, a nephropathy is almost invariably present, usually in the form of a chronic nephritis.

The destructive skeletal changes in simple acromegaly are minimal as a rule (osteoporosis, osteomalacia), being dominated by the constructive bony processes (skeletal overgrowth). In complicated acromegaly (parathyropituitary syndrome in pituitary eosinophilism), on the other hand, the reverse seems to be the rule in extreme cases. Bone resorption is much more intensive and may lead to pronounced osteoclastic phenomena accompanied by fibrous neoformation of osseous tissues.

Nephritis reinforces an apparently "primary" hyperparathyroidism resulting from or conditioned by a pituitary syndrome; consequently, secondary hyperparathyroidism is grafted onto the "primary" form. In this manner, the destructive processes are accelerated with corresponding increases in bony catabolism and pluri-hyperendocrinism.

Intermediate expressions of the parathyropituitary syndrome, ranging from one extreme to the other, may be found in pituitary eosinophilism.

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Granuloma of the Pituitary Associated with Pan-Hypopituitarism

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Reports of pituitary failure caused by granulomatous lesions are infrequent enough to warrant the presentation of such an example. Tuberculosis of the pituitary has been reported by a number of observers (1–3). Such lesions are usually associated with infection of the central nervous system or other systemic infection. Tuberculosis of the pituitary has also been reported as an isolated lesion. Noteworthy among these reports is one by Coleman and Meredith (4) who observed a case of diffuse non-caseous tuberculosis of the pituitary associated with enlargement of the sella turcica, primary optic atrophy and bitemporal hemianopia in which the growth-simulated tumor of the pituitary body and in which the post-operative period of survival had been $3\frac{1}{2}$ years at the time of reporting. Boeck's sarcoid has also been observed in the pituitary (5) and such a lesion cannot always be differentiated from a tuberculoma.

The case here reported presented marked pan-hypopituitarism with febrile episodes simulating in some respects the case reported by Dynes (6). The latter observed a patient with a calcified pituitary tumor with myxedema, episodic hyperthermia and stupor. Our patient was first suspected of having a chromophobe adenoma, but the febrile course of the disease compelled consideration of tuberculosis or Boeck's sarcoid as the underlying pathology.

The patient *H. L.*, age 54, was admitted to the hospital in December, 1942 for the study of a refractory macrocytic anemia. He stated that he had not been well since an attack of "influenza" 19 years before. This was said to have been complicated by pleurisy, which was subsequently diagnosed tuberculous. The pulmonary lesion became quiescent and the patient was able to resume partial activity. His health began to fail nine years ago and since that time he has become progressively more debilitated with weakness, arthralgia, headaches and failing vision in the right eye. About seven years ago he had a "pneumonia" associated with hemoptysis. At this time macrocytic anemia was diagnosed. The anemia was, however, unresponsive to the usual liver and iron therapy. Thyroid had also been prescribed because of a low basal metabolic rate and intolerance to cold. This he tolerated poorly. Because of failure to attain any improvement he was admitted to the hospital for study.

On admission he complained of progressive asthenia, loss of libido and body hair, intolerance to cold, severe migranous headaches with nausea and vomiting, and progressive failure of vision associated with pain in the right eye. Throughout the first period of observation in the hospital the temperature was normal. There was no apparent cardio-respiratory difficulty. His appetite was fairly good. There was no soreness of the mouth or tongue. The bowels were occasionally loose. In addition to weakness the patient was conscious of muscular twitching in the lower extremities as a result of which he walked rather sluggishly with the help of a cane.

In 28 years of marriage one son was born, 17 years ago. Libido was normal until 9 years ago since which time he has been impotent.

There were no other items in the patient's or the family history which appeared to be of relevant interest.

Examination revealed a sallow, somewhat lethargic male. His height was 66 inches and weight 125 pounds. The temperature and pulse were normal. The habitus was moderately eunuchoid (fig. 1). The blood pressure was 110, systolic and 70, diastolic. Body hair was completely absent though scalp hair was relatively abundant. The skin was thick but of soft texture. The right eye was non-reactive to light because of a glaucoma and vitreous opacities in the anterior chamber. The left eye was normal. There was no lymphadenopathy. There were no adventitious breath sounds in the chest. Heart tones were distant. No masses or focal tenderness were evident in the abdomen. Both testes were atrophic. The prostate was small and hard. The penis

was smaller than average. Muscle tone was poor. A neurological examination revealed no abnormal findings. The visual field studies could not be made because of the blind right eye.

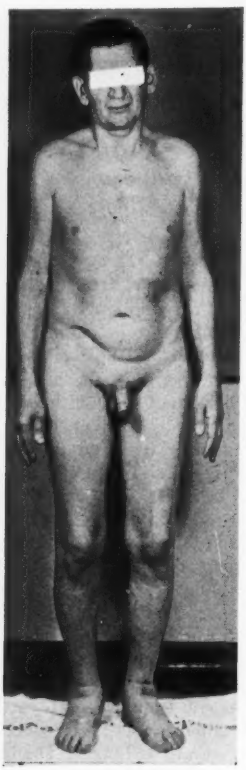

FIG. 1. H. L., the patient at age 54.

The pertinent laboratory findings on admission may be summarized.

Blood data: Hemoglobin 69—78% (Sahli); Color index, 0.8–1.1.
Erythrocytes, 3,500,000–3,800,000 per cu. mm. with occasional macrocytes and microcytes.
Leucocytes, 4,000–6,700 per cu. mm.
Reticulocytes, 1–2%.
Volume index, 0.78.

Gastric analysis revealed an absence of free hydrochloric acid with low total acidity.
Sternal biopsy showed normal bone marrow.
An electrocardiogram revealed the characteristic low voltage pattern of myxedema.

B.M.R.	−35%
Serum cholesterol,	249 mg. %
Serum albumin,	4.3 mg. %
Serum globulin,	2.6 mg. %
Serum sodium,	294 mg. %
Serum potassium,	21.4 mg. %
Serum calcium,	8.5 mg. %
Serum phosphorus,	3.5 mg. %
Serum phosphatase,	6.4 Bodansky units.
Urea clearance	30 %
Urinalysis	negative.
Glucose tolerance	(100 mg. glucose)

Hours	F[1]	1	2	3	4
Mg. glucose per 100 cc. blood	104	145	168	161	141

Urinary gonadotropins,	none recovered
Urinary estrogen,	none recovered
Urinary 17-ketosteroids,	2.5 mg./24 hours.

An x-ray plate of the sella turcica showed intra-sellar calcification with intact clinoid processes.
Fluoroscopy of the chest and gastro-intestinal tract revealed essentially normal findings.
Insulin tolerance[2]

Minutes	(*mg. glucose per 100 cc. blood*)
Fasting	115
20	128
30	130
60	128
120[3]	100
145	106
160	82

Thus, in support of the diagnosis of panhypopituitarism was the obvious clinical evidence of the failure in the functions of the thyroid, adrenal cortex and testes in addition to the laboratory findings of a macrocytic anemia and the almost total absence of the urinary steroid hormones. However, neither the glucose nor the insulin tolerance curves were typical of pituitary failure. There was nevertheless enough clinical and laboratory evidence to substantiate the diagnosis.

The patient was discharged with the following substitution therapy: a) thyroid, 1 grain and methyl testosterone, 20 mg. daily; b) optimal diet with added salt, 6–8 gm. daily.

He responded well to this ambulatory regimen so that he began to regain some weight and energy and complained of fewer headt aches with only occasional pain in the righ eye. However, he returned about one month later complaining of fever, prostration, anorexia, and diarrhoea. He was promptly readmitted to the hospital with an impending Addisonian crisis. The temperature varied from

[1] Fasting.
[2] Eight units crystalline administered.
[3] Epinephrine (1–1000) 0.4 cc. administered.

99°–101°F. The blood pressure fluctuated between 90 and 100, systolic, and 50 and 60, diastolic. The serum sodium was 276 mg.%. Urinalysis showed acetone. He was promptly given intravenous glucose in physiologic saline solution and 10 mg. desoxycorticosterone acetate intramuscularly. Through oversight cortin was not administered. The intravenous fluids and the desoxycorticosterone were continued daily or every other day until the diarrhoea and the prostration were beginning to improve. Serum sodium increased to 287 mg.% and the blood pressure rose to 110, systolic and 70, diastolic. The patient, however, remained critically ill with daily fever up to 101°F. Though diarrhoea had abated, anorexia limited the food intake so that intravenous glucose and salt infusions had to be given occasionally. Fluoroscopy of the chest revealed an acute infiltration in the right hilum. This soon extended into the parenchyma of the lung. The Mantoux test was strongly positive. Gastric washings twice revealed acid-fast bacilli. The sedimentation rate was greatly accelerated. The leucocytes varied from 6,000 to 6,900 per cu.mm. Tests for typhoid and paratyphoid were negative. Brucellergin induced a mild skin reaction. Blood cultures remained sterile.

The patient continued a febrile downhill course with progressively increased debility and asthenia. He finally became stuporous and died approximately one month after the final admission.

Post-mortem examination revealed the following findings: moderate atrophy of the skeletal musculature, considerable coronary arteriosclerosis and myocardial fibrosis, moderate chronic atrophic gastritis, moderate focal fibrosis of the liver, moderate diffuse subacute lymphadenitis, perhilar and peribronchial inaltration with intense bilateral pulmonary congestion and edema. There were also considerable focal fibrosis and apical pleural adhesions. In the posterior portion of the right upper lobe was found a well circumscribed nodule measuring 2 cm. in diameter and composed of a cheesy, whitish-gray material. A fairly extensive, peculiarly dense, yellowish-white, fine-textured infiltration in the hilus of the right lung was found to surround several of the main branches of the pulmonary artery and extended along the bronchi for several centimeters into the lung parenchyma. In these areas there was calcification and necrosis of the infiltrating mass. Microscopically these infiltrations were granulomatous in character—some with caseous necrosis and marked peripheral fibrosis but showing relatively little round-cell infiltration and no giant cells (fig. 2).

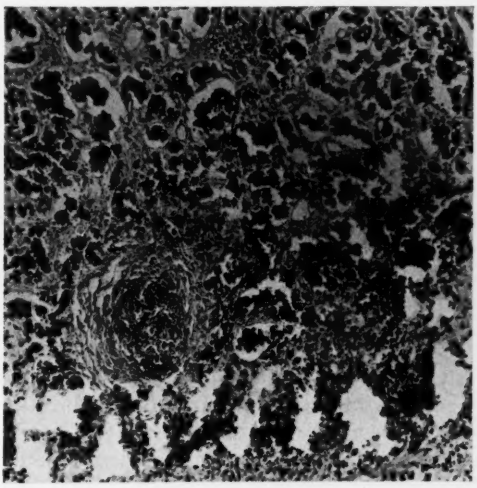

FIG. 2. Microphotograph of a section from one of the granulomatous nodules seen in the lungs. Sections from the anterior lobe of the pituitary gland were not available for comparison.

The endocrine system showed: 1) a fibrous and partially calcified granulomatous lesion of the pituitary; 2) marked atrophy of the testes with considerable atrophy of the prostate and of the epididymis; 3) considerable atrophy of the thyroid; 4) considerable atrophy of the suprarenals; 5) considerable atrophy of the pancreas with focal and diffuse fibrosis.

Microscopially the pituitary revealed an unusual lesion; only a very small formation of the original architecture was visible. The tissue was composed of anterior-lobe cells. These cells were small, though chromophobes, eosinophiles and basophiles were recognizable. Approximately nine-tenths of the original stroma was replaced by dense scar tissue with focal calcification and, in places, bone formation. In two of the sections between masses of calcium, the tissue appeared caseous and thick. The scar

tissue at the periphery showed only slight round-cell infiltration. None of the intermediate lobe could be identified. A very small portion of the posterior lobe could be seen in one area. Two additional sections with Ziehl Neelsens' stain revealed no acid-fast baccili.

The suprarenal glands showed marked atrophy. The medulla was almost completely replaced by a large amount of pink-stained hyalin material. The cortex was extremely thin, The remaining cells were not remarkable but were widely separated by interstitial fibrosis. There was slight, diffuse round-cell infiltration.

The anatomical diagnosis of the basic pathology was that of granulomatous infiltrations in the lungs and in the anterior pituitary.

COMMENT

Whether the basic lesions were tuberculous or those of Boeck's sarcoidosis could not be determined with certainty. Although no acid-fast bacilli were observed in any of the tissue sections, some were found in two different specimens of gastric washings. The latter finding suggested that the granulomatous lesions in the lungs and in the pituitary may have been of tuberculous origin. Yet Berblinger isolated in a case of Boeck's disease tubercle bacilli from guinea pigs inoculated with tissue from pulmonary lesions similar to those herein reported. It is not within the province of this clinical report to attempt the differentiation of this controversial granulomatous lesion. However, many features observed in this case and in other case reports are strongly suggestive of an atypical tuberculosis.

Regardless of whether the disease be tuberculous or Boeck's sarcoid, the granulomatous infiltration did largely destroy the pituitary to give the classical picture of pan-hypopituitarism. Death apparently followed an Addisonian crisis precipitated by a reactivation of an arrested chronic pulmonary infection. It is apparent from the post-mortem findings that the chief target organs—the thyroid, the adrenals and testes—failed in their function by virtue of atrophy secondary to the pan-hypopituitarism. This outcome follows the classical pattern of Simmonds' disease. Ordinarily the functional failure manifested in this endocrinopathy is amenable to symptomatic relief with replacement organotherapy (8–10) but when the disease is complicated by such widespread infection and especially by a fulminating pulmonary infiltration the added burden is apt to hasten adreno-cortical failure. Likewise, this infection seemed to nullify the therapeutic efforts during the terminal illness of the patient. It is possible that higher dosage of desoxycorticosterone supplemented with adequate cortin might have prolonged life; but in the presence of so much acute and chronic infection organotherapy seemed destined to be of limited value.

SUMMARY

A middle-aged, white man developed classical pan-hypopituitarism incident to the development of a granulomatous type of lesion characteristic of either an atypical tuberculosis or Boeck's sarcoid.

Exact differentiation of the lesion was not possible. Death followed acute adreno-cortical failure, precipitated by fulminating pulmonary invasion with the same granulomatous lesion found in the anterior-pituitary gland at autopsy. Post-mortem examination revealed in addition marked atrophy of the adrenal cortex, both testes and the thyroid.

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Parathyroid Insufficiency and the Human Electroencephalogram

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Serial electroencephalograms were made on 17 patients who presented various evidences of parathyroid insufficiency. The group included cases of: a) spontaneous parathyroid insufficiency; b) post-surgical parathyroid insufficiency; c) post-surgical or spontaneous parathyroid insufficiency treated by grafting of parathyroid glands; d) parathyroid insufficiency combined with manifestations of epilepsy.

TECHNIQUE

A three-channel Grass ink-writer electroencephalograph was used. Tracings were taken with push-pull recording using Gibb's technique (1) following a period of over-breathing. Hyperventilation was uniform in all cases, namely, 30 deep breaths in 45 seconds. We had previously determined that such a procedure does not significantly change the electroencephalogram in normal subjects. Medical treatment of the parathyroid insufficiency consisted in calcium lactate by mouth, calcium gluconate intravenously, vitamin D_2 and parathormone. Surgical treatment consisted in the

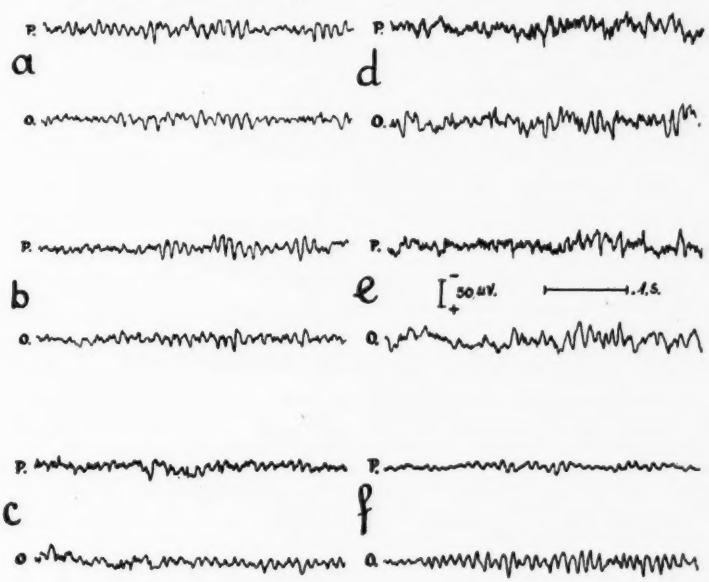

Fig. 1. Electroencephalograms in a case of spontaneous parathyroid insufficiency.

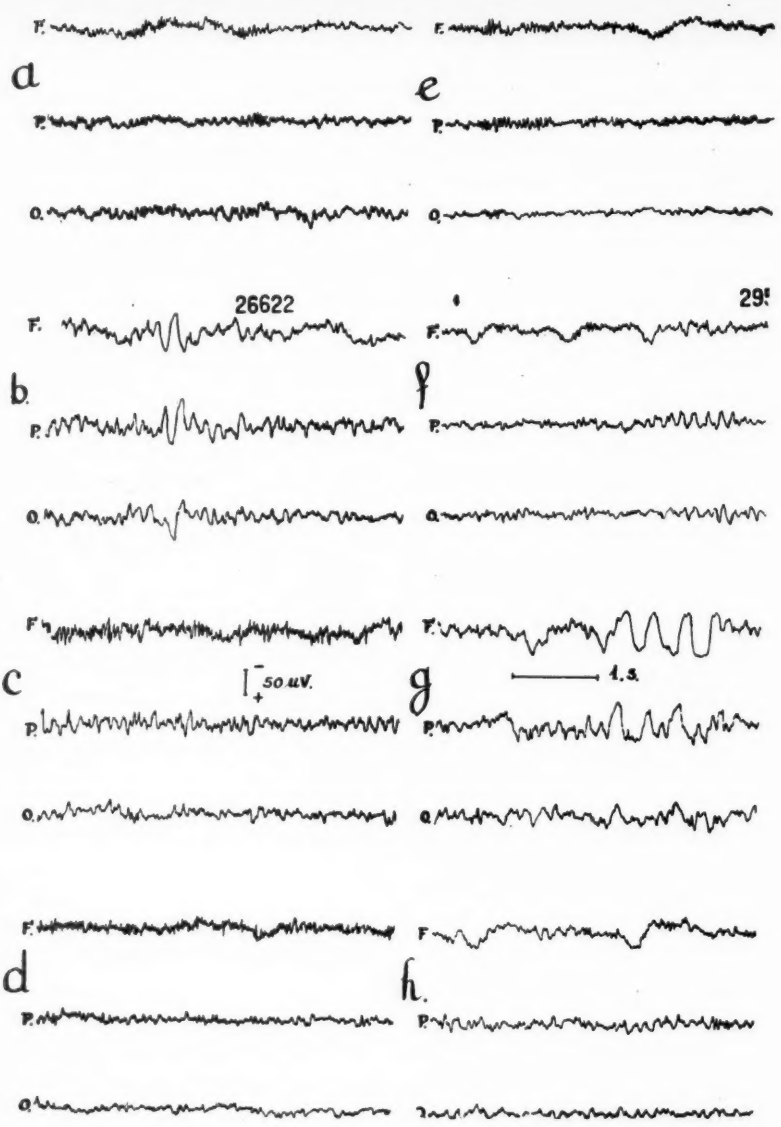

FIG. 2. Electroencephalograms in a case of post-surgical parathyroid insufficiency.

grafting of human parathyroid gland (Manfredi and del Castillo, 2).

A. *Spontaneous Parathyroid Insufficiency.* We shall describe one of the two cases studied.

Lon H. had suffered for four years with spontaneous tetany. He had been treated with calcium, parathormone and vitamin D_2. The blood calcium was 7 mg. per 100 cc. of serum. The electroencephalogram taken 24 hours after abundant administration of calcium by mouth was normal; Alpha rhythm of 10 per second and 35 microvolts and Beta rhythm of 22 per second and 7 microvolts (fig. 1a) were registered. The intravenous injection of 0.4 gm. of gluconate did not change the tracing (fig. 1b). The treatment was suspended and a week later the electroencephalogram (fig. 1c) presented a Beta rhythm in the parietal region more persistent and of a higher voltage than before, the Alpha rhythm being diminished. Hyperventilation (fig. 1b) increased the parietal Beta rhythm in amplitude and

constancy. In the occipital record the Beta modulated the Alpha rhythm, which tended to disappear. Short-lasting groups (3–4 waves) of a frequency of 6–7 per second can be seen in the occipital and parietal records (fig. 1e). Four months later, when the patient was feeling very well, the electroencephalogram did not show the fast waves in the parietal and occipital regions (fig. 1f).

In both cases of spontaneous parathyroid insufficiency, in the electroencephalogram there was a tendency for the Alpha rhythm to be absent and to be replaced by a fast rhythm of variable voltage, the frequency of which was higher than that of the usual Beta rhythm. Even in the moments when the blood calcium and the electroencephalogram were apparently normal as a result of the treatment, standard hyperventilation produced this type of alteration in the tracings. When 0.4 gm. or even 1.5 gm. of calcium gluconate was injected there was no alteration in the tracing. Short-lasting groups of slow waves of 6–7 per second could be seen.

B. *Post-Surgical Parathyroid Insufficiency.* Seven cases were studied. The time elapsed between thyroidectomy and our observation varied between 12 days and 3 years. All cases presented clear signs of parathyroid insufficiency. One case will be described briefly.

Rie C. was seen 15 days after throidectomy when nervousness and a positive Chvostek sign were present. A paroxysmal series of Beta rhythms in the three leads (frontal, parietal and occipital) was seen. Alpha rhythm was practically absent in the occipital record (fig. 2a). The blood calcium at this time was 9 mg. per 100 cc. of serum. Hyperventilation gave isolated trains of slow waves of decreasing intensity in the anteroposterior direction (fig. 2b) with exaggeration of the discharge of Beta waves in the three leads (fig. 2c). Five minutes later the record had recovered the initial characteristics (fig. 2d). Three months of intense treatment were followed by its suspension during 35 days, when the typical electroencephalogram of insufficiency shown in figure 2e was taken. Notable were absence of Alpha rhythm and paroxysmal Beta discharges in the three standard records. At that time the blood calcium was 8.6 mg. per cent. Eighteen seconds of hyperventilation produced slow waves in the fronto-parietal leads (fig. 2f). At the end of this procedure these waves were more constant and decreased in amplitude from the frontal region towards the occipital pole (fig. 2g). Some minutes afterward the tracings were similar to those at the beginning (fig. 2h).

In all the seven cases, when the medical treatment produced a clinical and electroencephalographic disappearance of the signs of insufficiency, the hyperventilation brought them back; when they were already present in the electroencephalogram, this procedure grossly intensified them.

C. *Post-Surgical or Spontaneous Parathyroid Insufficiency Treated by Grafting of Parathyroid Glands.* Six cases were studied. The time elapsed between the appearance of the insufficiency and the grafting varied from 8 months to 11 years. Some of the patients have been observed for more than two years after the grafting.

The graft of parathyroid gland from a newly-born child when properly made (2) has had a remarkable effect—a clinical and electroencephalographic compensation. In some cases (apparently due to reabsorption of the graft) after about a year some signs of defect could be found in the tracings, especially with the hyperventilation. Two cases, one observed 55 days and the other 2 years after the implantation, will be described.

Fer. N. suffered from exophthalmic goiter. Thyroidectomy had been performed in 1936. A short time afterward a complete clinical picture of a serious parathyroid insufficiency appeared. Intense medical treatment failed to keep the patient constantly in good condition. Six years after the thyroidectomy and during intense treatment the electroencephalogram was almost normal for some moments (fig. 3a) and at times presented a slow paroxysmal rhythm of 66 per second and 80–100 microvolts in the parietal leads (fig. 3b). With hyperventilation, occipital Alpha rhythm disappeared in part or showed itself modulated by the faster rhythm (fig. 3c). Thirty seconds after the end of the hyperventilation these characteristics were still present (fig. 3d). A fortnight afterward the blood calcium was 7 mg. per cent. Seven and one-half months after the last records a graft of foetal parathyroid gland was implanted following Manfredi's technique (2). Twenty days after the operation the blood calcium was 8 mg. per cent. Thirty-four days after the operation the patient felt perfectly well; she was clinically normal and the electroencephalogram was normal both before (fig. 3e) and after the hyperventilation (fig. 3f).

Abr. A. had undergone thyroidectomy five years previously. Some months afterward complete signs of parathyroid insufficiency appeared. The usual clinical treatment produced only partial and temporary relief. Two years ago a graft of parathyroid gland was made. Since then, no subjective or objective clinical signs of parathyroid insufficiency have been evidenced. The electroencephalogram was quite normal both before hyperventilation (fig. 4a and 4c) and after it (fig. 4b).

D. *Parathyroid Insufficiency Combined with Manifestations of Epilepsy.* Two cases were studied. Both will be described briefly.

Pen. R. manifested tetanic fits alternating with typical "grand mal" seizures. The record showed what somewhat the type of the true slow epileptic waves [3-per-second rhythm of Gibbs (1) and Jasper (3)]. Later on the hyperventilation gave typical epileptic sub-clinical discharges of 3-per-second spikes and slow waves (fig. 5c).

Obviously we were dealing with a parathyroid in-

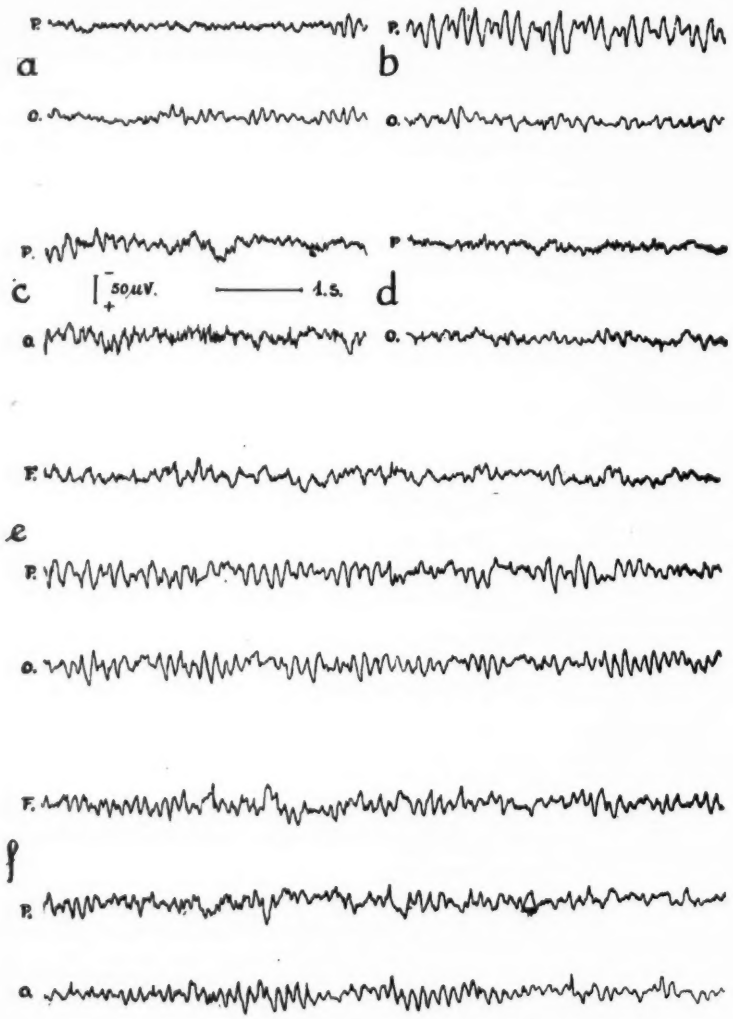

FIG. 3. Electroencephalograms in a case of parathyroid insufficiency treated by grafting parathyroid glands of a newly-born child.

we usually see in cases of parathyroid insufficiency: fast rhythms were prominent and Alpha rhythms, absent or nearly so (fig. 5a). The blood calcium at that time was 9 mg. per cent. Hyperventilation caused the appearance in all three records of slower waves (2–3 per second) than those seen by us in our cases of parathyroid insufficiency (fig. 5b); such waves had

sufficiency in an epileptic patient. The epileptic manifestations became more evident with hyperventilation as is usual in such cases.

Tis. H. had undergone thyroidectomy four years ago. Shortly afterward signs of parathyroid insufficiency appeared. She was treated intermittently with parathormone and calcium following which slight

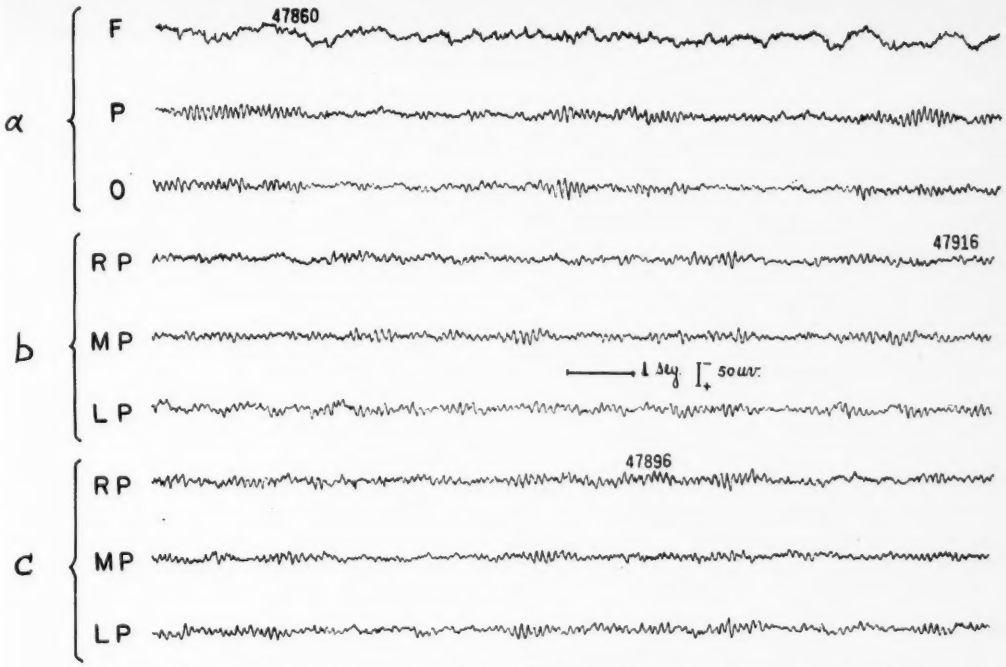

FIG. 4. Electroencephalograms in case of parathyroid insufficiency treated by grafting of parathyroid glands of a newly-born child.

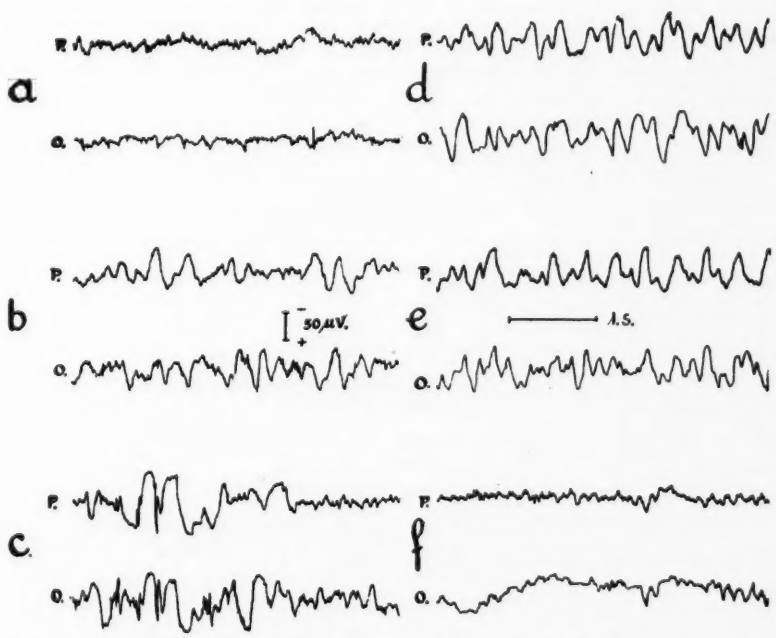

FIG. 5. Electroencephalograms in a case of parathyroid insufficiency combined with manifestations of epilepsy.

clinical improvement ensued. Two years ago a parathyroid graft was implanted, after which she was very well for nine months, when signs of parathyroid insufficiency began to reappear together with typical epileptic fits. The electroencephalogram was the usual one seen in chronic epilepsy with cortical disintegration: slow, 3-per-second, irregular waves all over the cortex (fig. 5d). A similar record was obtained a week later (fig. 5e). Hyperventilation gave the already mentioned changes seen in parathyroid insufficiency (fig. 5f). The blood calcium 25 days after this record was taken was 9 mg. per cent.

There is no doubt that this was a case of epilepsy in a person with clinical signs of parathyroid insufficiency, as can be seen in the spontaneous record. The signs of parathyroid insufficiency were evident in the electroencephalogram after the hyperventilation.

DISCUSSION

The electroencephalograms of adult men can be classified into several types (Davis and Davis, 4) with respect to the proportion of the record occupied by the Alpha rhythm; but in all our cases the faster rhythms were seen between the Alpha waves and not as a modulation of them.

In the patients with signs of parathyroid insufficiency (post-surgical or spontaneous) the electroencephalogram presents the following signs, all or part of which may be present and which are called electrical signs of the parathyroid insufficiency: a) a tendency of the Alpha rhythm to diminish or disappear in the occipital, parietal and frontal leads; b) an increase in amplitude and in constancy of the Beta rhythm which can appear uniform, paroxysmal or as modulating the Alpha rhythm; c) sometimes small spikes; d) groups of 2–3 slow waves of a frequency of 6–7 per second, more marked in the frontal than in the parietal leads.

In a normal man a hyperventilation of 30 inhalations in 45 seconds does not produce noticeable modifications in the electroencephalogram. In all patients with clinical parathyroid insufficiency the above test in our experience has been positive. In those cases in which the encephalogram was kept normal by therapeutic means the characteristic hypoparathyroid pattern could be induced by the over-breathing. In cases in which evidence of the insufficiency was initially present, hyperventilation caused an exaggeration of the pattern. Lehman (5) proved that alkalosis augments the hyperexcitability of the nervous system; the effect of hyperventilation on the cortical potentials is to be regarded as a special case of the Lehman phenomenon.

The most striking signs of parathyroid insufficiency are seen in the electroencephalogram 15 days after surgical thyroidectomy. Under treatment they are not so evident. Calcium, parathormone and vitamin D_2 maintain the electroencephalogram in normal status, but always hyperventilation or the suspension of the treatment for a few days serves to bring out the characteristic modifications.

We have found a fair correlation between the subjective feeling of the patients with respect to their symptoms and what we have seen in the electroencephalogram.

In all our patients the total serum calcium was under 10 mg. per cent but we have not yet succeeded in establishing a clear relation between the extent of the disturbances in the electroencephalogram and diminution in the serum calcium.

The characteristic rapid rhythm of 20–25 oscillations per second which is already present 12–15 days after the initiation of the parathyroid insufficiency is within the frequency of the Beta rhythm of normal persons. Such rhythms are much like the spikes seen in paroxysmal epilepsy but of smaller voltage. This resemblance appears more convincing in that the patients with parathyroid insufficiency spontaneously show some spikes and bursts of slow waves and these become more evident after hyperventilation, as is known to happen with the epileptic manifestations. Furthermore, in our cases there was an unmistakeable association, clinical and electroencephalographic, between tetany and epilepsy. One of our cases gave a typical record of epilepsy and hyperventilation produced the manifestations which we interpret as parathyroid insufficiency; in another with a record of parathyroid insufficiency the same procedure gave opposite results.

That the faster rhythm seen in the parathyroid insufficiency is not an artifact due to muscle contraction during tetany is clear because muscle action currents are faster and they can be seen neatly separated from the

Beta rhythm in cases with poor compensation, when the hyperventilation provokes clinical tetany.

Parathyroid grafts serve to correct the electroencephalographic manifestations of parathyroid insufficiency. In some cases there is some reappearance of them after six months. Obviously in such cases there is a slow partial reabsorption of the graft, but calcium and vitamin D_2 then easily compensate the deficiency. When the graft is properly made and there is no reabsorption a complete disappearance of all the objective and subjective deficiency manifestations can be observed. Concomitantly with this practical cure (3 years in one case) an absence of all the deficiency signs in the electroencephalogram was seen.

Cortical functioning in cases of parathyroid deficiency has similar features with the cortical dysrhythmia pointed out in the epilepsies by Gibbs, Gibbs and Lennox (6); the cortex behaves like a poorly regulated thermostat because, together with the normal rhythms, slower and faster ones can be paroxysmally present.

SUMMARY AND CONCLUSIONS

Seventeen patients with spontaneous or postsurgical parathyroid insufficiency presented several electroencephalographic manifestations, which were present individually or in combination. These manifestations are the following:

1. A marked tendency of the Alpha rhythm to diminish or disappear in the occipital, parietal and, to lesser degree, in the frontal records.

2. An increase in constancy and amplitude of the Beta rhythm; it can be uniform, paroxysmal or appear as a modulation of the Alpha rhythm.

5. Presence of simple spikes.

4. Groups of 6–7 slow waves of a frequency of 2–3 per second appearing mostly in the fronto-parietal leads.

In all those cases in which medical treatment had corrected the signs of clinical insufficiency a hyperventilation of 45 seconds evoked in the electroencephalogram the above-mentioned signs.

Parathyroid grafts (glands of human newly-born) normalized the clinical and electroencephalographic manifestations of insufficiency. In the cases in which the graft was reabsorbed the signs gradually reappeared. When the graft remained active (three years in one case) the electroencephalogram was normal even after hyperventilation.

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The Antihormone Problem in Clinical Endocrine Therapy

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VARIOUS clinical syndromes which are diagnosed as due to the hypofunctioning of an endocrine organ frequently necessitate the administration of substitution therapy for considerable periods of time. Certain therapeutic measures involve the injection of extracts containing proteins of heterologous source and in these instances antagonistic factors (antihormones?) may form in the blood stream to negate the action of the injected hormone and perchance to cause anaphylaxis. The majority of investigations on this subject involve the study of experimental animals and recent reviews (Collip, *et al.*, 1; Thomson, *et al.*, 2; Thompson, 5) discuss the matter thoroughly. The present report, however, deals primarily with the clinical aspects of this problem.

Clinical use of insulin in diabetics during the past 20 years shows that refractoriness to insulin is rare. Cases of refractoriness to insulin therapy in man have been reported but it is generally thought that this refractoriness is not antihormonic in nature. However, in a recent study on insulin resistance, Lerman (4) reports that antibodies to insulin in man appear to be antihormonic.

Protracted treatment with either sex hormones or adrenal cortical extract rarely produces antagonistic factors in man. The sex hormones and the cortical substances are steroids to which refractoriness may result but to which the formation of antibodies is unlikely. Rowntree (5) has cited three cases of Addison's disease surviving for 15 years on cortical extract. The life-maintaining activity of desoxycorticosterone acetate is now well known with no report of refractoriness. It should be pointed out that Hartman and his associates (6) have observed refractoriness to adrenal-cortical extract when administered to dogs although treatment with corticosterone was devoid of this action.

Parathyroid preparations belong to the protein group and have been reported to lose hypercalcemic activity following protracted therapy in man (Selye, 7). The possibility of a parathyroid anti-factor has been considered by Levy-Simpson (8) although Taylor, Weld and Sykes (9) presented experimental proof that the hormone refractoriness is not due to an antisubstance in the serum.

ANTITHYROID SUBSTANCES

Factors which are antagonistic to the action of thyroid secretions have been obtained. Ballet and Enriquez (10) fed the serum from thyroidectomized dogs to patients suffering from Basedow's disease and claimed beneficial results. In similar fashion, Burghart and Blumenthal (11) fed the serum from myxedematous patients to individuals with exophthalmic goiter and observed favorable results. Mobius (12) obtained beneficial results in patients with Basedow's disease by feeding the blood from thyroidectomized sheep. More recently, Blum (15) reported on an antithyroid substance which he termed "Katechin" which he claimed was present in all normal blood. Anselmino and Hoffman (14) showed that "Katechin" was absent in Graves' disease. A number of other investigations on this subject are omitted since these antithyroid substances appear to be different from antihormones in that they are active on oral administration and are probably not proteins.

A number of investigations have been made on the human patient suffering from hyper-

thyroidism to determine whether antibody formation occurs in this disorder. Complement fixation reaction and precipitin formation were the methods employed but the results are contradictory. The existence of an antithyroid substance in the antihormonic sense is not as yet proven.

Rogers and Beebe (15) initially attempted to treat patients suffering from exophthalmic goiter by means of an antiserum to human thyroid. Animal experimentation by Lerman (16) showing that mammalian thyroglobulin is strongly antigenic leads him to suggest that antiserum treatment of Graves' disease should be re-evaluated.

ANTAGONISTIC FACTORS TO EXTRACTS FROM THE ANTERIOR PITUITARY GLAND

A number of factors have been extracted from the anterior lobe of the pituitary. These include gonadotrophic, thyrotrophic, growth, adrenotrophic, lactogenic and varied metabolic factors. These hormones are considered to be protein in nature and protracted treatment would present the possibility of antagonistic substances developing in the serum. Most of these hormones have been given limited clinical trials and data regarding their antigenicity in the human are wanting. Results from experimental animals, however, indicate that antagonists to these injected extracts will develop. Sufficient clinical data are available on the thyrotrophic and gonadotrophic hormones to warrant their further discussion.

Antithyrotrophic Substances

The spontaneous occurrence of antithyrotrophic factors in the blood of individuals not previously treated has been described by Collip and Anderson (17), Herold (18a and b), Eitel (19), Simon (20) and Picado and Rotter (21). Furthermore the concentration of antithyrotrophic factor has been found to be subnormal in Graves' disease (Blum, 15, 22; Herold, 18a and b; Spence and Scowen, 23; Scowen and Spence, 24; Eitel, 19a) whereas this factor is increased in cretinism (Saegesser, 25; Hara, 26; Picado and Rotter, 21a and b). In cases of Graves' disease relieved by treatment, the amount of antithyrotrophin rises (Fellinger and Schlesinger, 27a and b; Bodard and Fellinger, 28).

Substances antagonistic to thyrotrophic hormone have been found in a case of Cushing's syndrome (Eisenhardt and Thompson, 29). Mueller (30) and Neuweiler (31) reported that more antithyrotrophin was present during pregnancy than normally but Anselmino and Hoffman (14) reported just the opposite finding.

Substances antagonistic to a thyrotrophic preparation have been shown to develop in man following treatment with this extract (Spence and Witts, 32).

Antigonadotrophins

Are antigonadotrophic factors normally present in man? Antigonadotrophins have been detected in the blood of 10 normal, untreated individuals (Collip, 33, Collip and Anderson, 17); in amenorrheic women (Takahashi, 34) and in a case of Cushing's syndrome (Eisenhardt and Thompson, 29). Laroche and Simonnet (35) detected antagonists to urinary gonadotrophins in the sera of an ovariectomized woman and in an oligomenorrheic woman. On the other hand, there is considerable evidence that factors which are antagonistic to gonadotrophic hormones are not present in the blood of humans. Fellows (36) tested the sera of normal women for antagonistic substances against human pituitary and obtained negative results. Zondek and Sulman (37a and b) did not find antigonadotrophins to chorionic or menopause urine gonadotrophins in the sera of normal patients. Similar results have been reported by Eisenhardt and Thompson (29) and by Hauptstein and Otto (38). Laroche and Simonnet (35) and Zondek and Sulman (37b) failed to find substances inhibitory to urinary gonadotrophin or chorionic gonadotrophin in the sera of menopausal women.

Studies to determine whether inhibitory substances were present in the blood of women suffering from primary amenorrhea, secondary amenorrhea or sterility failed to reveal their presence in tests against chorionic and menopausal-urine gonadotrophin (Zondek and Sulman, 37b). Leathem and Abarbanel (39a and b) tested the sera from 39 primary or secondary amenorrheic women and one hypogonadal male for the presence of factors inhibitory to equine gonadotrophin (PMS). These tests were uniformly negative. More recently the sera of six

amenorrheic women have been tested against a preparation of sheep anterior-pituitary extract plus chorionic gonadotrophin[1] and no antagonistic action has been observed (Leathem and Abarbanel, 39c).

The high titre of chorionic hormone during pregnancy would appear to present optimal conditions for the spontaneous development of antagonistic substances. Antigonadotrophins related to chorionic gonadotrophin, however, have not been detected during pregnancy or within a month following paturition (Fluhman, 40; Eichbaum and Kinderman, 41; Kabac, 42; Zondek and Sulman, 37a).

Chorionic gonadotrophin and the antigonadotrophin problem

There is general agreement that the clinical use of chorionic gonadotrophin does not result in antigonadotrophin formation even when treatment is extensive. The failure of antagonistic factors to develop in the blood has been reported in each of the following clinical studies. Twombly (43) studied three patients injected with a preparation of chorionic gonadotropin from pregnancy urine,[2] 100 R.U. daily, one patient being treated for more than a year. Sulman (44) reported on three cases of which two males had received 12,000 R.U. during a 9-month period. Spence, Scowan and Rowlands (45) treated nine patients, 10 to 20 years of age, to induce descent of the testis. Dorff (46) obtained good clinical results in treating 19 boys, age 7 to 13, for genital under-development. One patient received as much as 112,300 R.U. in a 17-month period. Saphir, Howell and Kunstadter (47) treated nine boys and three adults but a 2800-R.U. total was the maximum dosage administered. Brandt and Goldhammer (48) previously reported on the failure of antagonists to develop in patients treated with A.P.L.

The clinical use of chorionic gonadotrophin is restricted since human ovaries show no follicular stimulation following its administration and follicular development may actually be arrested (Hamblen, 49). However, its use in the correction of cryptorchism is warranted since descent of the testis will result in a large percentage of cases while other cases in which surgical intervention will be required will be indicated.

Anterior-pituitary extracts and the antihormone problem

Obviously the extraction of human anterior pituitaries for gonadotrophic hormones to be used clinically is not practical hence pharmaceutical preparations of pituitary gonadotrophins are obtained from other animals. This involves, in therapy, the introduction of a foreign protein into the human blood stream and immediately suggests the possibility of antibody formation. Spence, Scowen and Rowlands (45) injected hog anterior-pituitary gonadotrophin and found the patients' sera to have an augumentative action after 16 and 21 weeks of therapy. This enhancing action of the serum disappeared at a later period but antigonadotrophins were not observed. On the other hand, antigonadotrophins have been established in the blood of human females injected with anterior-pituitary extract (Meyer and Sevringhaus, 50).

Recently a combination of sheep anterior-pituitary extract plus human chorionic gonadotrophin[1] has been approved for clinical use. It has been mentioned previously that the amenorrheic woman does not possess antagonists to this extract prior to treatment. Jailer and Leathem (51) failed to obtain antigonadotrophins in one patient tested six weeks after the first injection with the compound.[1] Further studies in two sterility patients over a longer period of time have also yielded negative results but at the same time no clinical improvement has been observed (Leathem and Abarbanel, 39). Reactions have been reported in patients receiving the compound, one patient having a severe anaphylactic reaction (Phillips, 52). Davis, Madden and Hamblen 53) noted local and constitutional reactions in a patient immediately following therapy although pre-treatment skin test was negative.

Mazer and Ravetz (54) indicated the stimulating effects of the compound[1] on the human ovary. Sufficient other positive responses have been reported since that time to warrant its clinical use but in protracted therapy the possi-

[1] The compound used was "synapodin" supplied by Parke, Davis and Company, Detroit, Michigan.

[2] "Follutein," prepared by E. R. Squibb & Sons, New York, N. Y., was employed.

ble development of antigonadotrophins and allergic manifestations must be considered.

Antigonadotrophins and equine gonadotrophin

Another very potent gonadotrophic extract available for clinical use is equine gonadotrophin (pregnant-mare serum). This preparation was received with favor when Davis and Koff (55) reported that ovulation of the human ovary could be induced with this hormone. However, a most important complicating factor from a clinical point of view is the development of antigonadotrophic substances. Rowlands and Spence (56) treated nine boys with equine gonadotrophin (PMS) and found antagonistic substances to be present in the serum four to six weeks after beginning daily or bi-weekly administration. They also found the titre of two patients rose three weeks after treatment was discontinued. Jailer and Leathem (51) obtained similar results in adult males and females treated for sterility although a 10-week interval after the first injection appeared necessary for the antigonadotrophins to form but they were detected at this time even though the entire course of therapy was given during one week. Antagonistic serum was obtained four months after cessation of treatment. Leathem and Abarbanel (39a and b) reported on a series of patients receiving PMS in which blood samples were obtained at varied intervals. Antigonadotrophins were first evident at 36 to 92 days (av. 63 days) after the first injection and persisted for at least three months after cessation of therapy. The hormone was administered during a 10-day period of each month's therapy. The titre of antigonadotrophic substances in one case, estimated by the use of smaller amounts of serum, was calculated on the basis of 50 cc. of plasma per kilogram body weight in a patient weighing 60 kg. The result indicated that the activity of 100,000 I.U. of hormone could be neutralized although only 8000 I.U. was administered during three courses of therapy. The same patient complained of dizziness, headaches, abdominal cramps and general malaise after each injection during the second and third courses of therapy, i.e., before and during the appearance of antigonadotrophins in her serum. Skin tests were uniformly negative. Allergic manifestations have been noted by other investigators (Fluhmann, 57; Erving, *et al.*, 58). The latter investigators reported three cases of positive skin test after one to five courses of PMS therapy and four patients complained of nausea, etc. Bickers (59) reported a case of near-fatal reaction to equine gonadotrophin. It should be emphasized that the presence of negative skin tests does not preclude the possibility of anaphylactoid reactions as the patient may be sensitized to certain substances in horse serum not necessarily the hormone.

When a more highly purified preparation of equine gonadotrophin (as indicated by nitrogen content) is used, the tendency for antigonadotrophic formation is markedly reduced. In fact, only one of 12 patients developed antibodies to this material and this result suggests that much of the antagonistic action is probably evoked by some extraneous protein material in the extract rather than by the hormone itself. With this more highly purified preparation treatment can be extended in necessary cases with less tendency for the formation of antisubstances (Leathem and Abarbanel, 39).

That the increased purity of a pituitary hormone will eliminate the antigenic problem in clinical therapy seems less likely since Chow (60) found that "pure" ICSH from hog-pituitary glands was antigenic and that the antiserum was species-specific and hormone-specific.

SUMMARY

Refractoriness or adaptation may occur in some clinical cases treated with non-protein hormones but this reaction is not considered an antihormonic response.

The existence of an antithyroid substance is still questionable although the use of antiserum in the treatment of Graves' disease has been proposed.

The clinical use of anterior-pituitary hormone necessitates the introduction of a foreign protein into the body and the resultant development of antibodies. Thyrotrophic preparations cause the development of antithyrotrophic substances in the blood but it is not known whether these substances are the same as those found in normal blood.

Clinical use of human chorionic gonado-

trophin has shown that this extract is not antigenic in man whereas equine gonadotrophin (PMS) will cause the formation of antigonadotrophins. Equine-gonadotrophin injections have been followed by anaphylactoid reactions which may be due to proteins in the extract other than the hormone. Increased purity of equine gonadotrophin reduced the tendency for the formation of antigonadotrophins. Evidence is not available to show that the combination of sheep anterior-pituitary extract plus chorionic gonadotrophin is antigenic in man.

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Eunuchoid Habitus Associated with Sickle-Cell Anemia and the Sickling Trait

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HEMATOLOGIC interest in sickle-cell anemia and the sickling trait has offered an opportunity to examine and study numerous subjects of this peculiar hemopoietic disorder. Since its recognition by Herrick in 1910, considerable clinical evidence has been recorded appertaining to its hemopathology and its associated bone changes. Little if any recognition, however, has been accorded the abnormal statural configuration of its subjects, which feature will be discussed in this report.

DESCRIPTION OF CLINICAL MATERIAL

Data on the statural characteristics of 32 Afro-American subjects are cited, 30 of whom had sickle-cell anemia. Of the remaining two, one showed the sickling trait only and another had an anemia without the sickling phenomenon but is included because of consanguinity to one of the patients in the sickle-cell anemia series. In only eight instances was it possible to examine other members of the patients' family. Since this number of families would be statistically insignificant, likewise a statistic on familial incidence of either the sickling phenomenon or any other coexistent anomaly would be vitiated.

MODE OF STUDY

The sickling phenomenon was determined in all cases by a wet, sealed preparation of the patients' blood observed for at least 48 hours at room temperature. Normal standards for comparison with the actual measurements of Age-Height (A-H), the Height-Span (H-S) and the Upper-Lower (U-L) dimensions are taken from Engelbach's tables (1). Blood counts were made with pipettes approved by the U. S. Bureau of Standards in a Levy-Neubauer counting chamber. Hemoglobin was determined by the Newcomer hemoglobinometer with a standard of 14.5 gm. of hemoglobin per hundred cubic centimeters of whole blood as normal.

STATURAL ASYMMETRY IN MALES

The male group consists of 13 of the 32 subjects of the study, none being in the infantile age classification although eight infantile offspring of members of this series have been examined.

Of the males recorded in the accompanying table, four were juveniles (six to 14 years of age), five were of adolescent age (15 to 20 years) and four were adults, ranging from 21 to 42 years of age.

The youngest juvenile, *Patient 31 Al* was six years of age, yet he showed a minor deviation of one inch increase in the lower extremity which was associated with an inch below the minimum normal for the upper segment. While this disparity is inconsequential at this age, a probable exaggeration of the U-L disparity in later years is suggested. A staturogram, figure 1, illustrates growth retardation and abnormal body configuration (*Patient 26 Wh*) far more convincingly than do the numerical data. (The normal standards in the staturogram are averages from Engelbach's table.) It is obvious that this patient's measurements, except the length of the lower segment, are to the left of his age group, hence below the minimum normal for his age. The asymmetry, not so evident in reading of two inches disparity, is remarkable when compared in the graph with the normal, which would be in a vertical position immediately below his age figure.

The second subject, *Patient 5 La*, 14 years, was staturally retarded and eunuchoid in habitus. The minimum normal H-S for his age is 58.6–59.6 inches while the actual was 54–56 inches with two inches difference in the U-L ratio. His weight, also, was six pounds below the minimum standard. The third juvenile, *26 Wl*, showed statural retardation comparable to *5 La* together with 11.6 pounds decrement in weight. The fourth patient, *24 Ho*, was markedly eunuchoid, showing lower measurements six inches greater than the upper.

The adolescent male group (15 to 20 years) consists of five patients ranging in age from 15 to 18 years. With one exception, *Patient 23 Bi*, the asymmetry of H-S and U-L ratios in the remaining four is so definite that comment is scarcely warranted. Within the group, however, is a eunuchoid giant, *Patient 13 Cl* (fig. 2), who had an H-S measurement of 76 and 83 inches respectively with a lower measurement exceeding the upper by nine inches. He will be discussed with his family series below.

The adult series of males comprises three mature subjects, *19 Ro*, *28 Do* and *30 Hi*, with a fourth, *21 Sw*, 21 years of age. In all instances however, their statural defects follow the regular pattern of the eunuchoid habitus.

All the males in this series had moderate to severe sickle-cell anemia. A roentgenogram of the skull of *Patient 23 Bi* (fig. 3) demonstrates the characteristic cranial osteoporosis almost invariably found in the anemic state of this hemopoietic disorder.

Age (Years)	7	8	9	10	11	12	13	14	15	16
Height (Inches)	46.8 / 47.2	48.9 / 49.2	50.9 / 51.2	53.0 / 53.2	55.3 / 55.2	57.6 / 57.1	59.7 / 58.9	61.4 / 60.7	62.5 / 62.4	63.2 / 64.0
Weight (Pounds)	47.2 / 48.1	52.0 / 54.8	57.4 / 58.0	63.6 / 64.3	72.4 / 71.2	80.6 / 78.3	90.0 / 85.8	101.4 / 92.0	107.7 / 101.4	110.9 / 109.0
Span (Inches)	46.0 / 46.1	48.2 / 48.6	50.4 / 51.0	52.6 / 53.4	55.3 / 55.6	57.5 / 57.9	59.7 / 60.2	61.3 / 61.9	63.0 / 64.1	63.6 / 65.8
Head (Inches)	20.3 / 20.6	20.4 / 20.7	20.5 / 20.9	20.7 / 21.0	20.9 / 21.1	21.0 / 21.2	21.2 / 21.4	21.4 / 21.6	21.6 / 21.8	21.7 / 22.0
Chest (Inches)	22.7 / 23.3	23.4 / 24.0	24.2 / 24.6	25.0 / 25.3	26.1 / 26.1	27.1 / 27.0	28.1 / 28.0	28.9 / 29.1	29.6 / 30.3	30.1 / 31.7
Waist (Inches)	20.5 / 21.3	20.8 / 21.8	21.2 / 22.3	21.8 / 22.8	22.4 / 23.3	23.2 / 23.8	23.9 / 24.6	24.5 / 25.4	24.8 / 26.4	25.1 / 27.2
Upper (Inches)	24.4 / 24.6	25.1 / 25.1	25.8 / 25.9	26.7 / 26.7	27.5 / 27.4	28.7 / 28.3	29.6 / 29.1	30.6 / 29.8	31.2 / 30.8	31.5 / 31.5
Lower (Inches)	22.6 / 22.4	23.6 / 23.8	25.1 / 25.1	27.7 / 26.3	27.7 / 27.6	28.8 / 28.7	29.9 / 29.9	30.9 / 30.7	31.3 / 31.7	31.5 / 32.5

N.B. Measurements for females are in upper and males in lower division.

FIG. 1. Staturogram showing a eunuchoid asymmetry of a juvenile having sickle-cell anemia.

STATURAL ASYMMETRY IN FEMALES

Statural asymmetry in the female series of sickle-cell anemia and sickle trait (see table) presents less latitude for controversy in the over-all pattern than that in the male series, since only one patient, *2 Ma*, had the minimum of one inch difference in the U-L ratio. At the same time she had two inches greater span than height although the significance of this small difference might be questioned.

The female series comprised 17 anemic patients, with an additional one showing the sickling trait without anemia and a second having

a severe anemia with questionable sickling, making a total of 19 females studied.

There were two patients, *7 Ad* and *8 Ad*, sisters in the juvenile age bracket (6 to 12 years). *Patient 7 Ad* had a questionable sickling, which because of poor cooperation was not established. Neither manifested secondary sex characters at the ages of 10 and 11, but their U-L ratios were both widely disproportionate, there being six and seven inches, respectively, greater length of their lower than upper segments.

The adolescent females were six in number and ranged from 13 to 18 years. They present no diagnostic problem as regards statural configuration since the disproportions are classical. Some data on the reproductive cycle have been recorded in the table for several members of this group. No attempt has been made to correlate the evidences of sex deviation, however, with the issue in this paper.

The adult series of females embraced the larger number of patients, there being 11 of an age range of 18 to 38 years. All were anemic except *11 Cl* who showed only the sickling trait. The disparity between Height-Span and Upper and Lower Segments is so great in the majority of this group that narration of the particulars would add nothing of interest. Underweight is a trend also, there being but one of the patients, *11 Cl*, who was overweight, and as remarked above, she was not anemic.

FAMILIAL OBSERVATIONS

The eunuchoid giant described above (*Patient 13 Cl*) should be compared also with *Patients 10 Cl*, *11 Cl* and *12 Cl*, his mother and two sisters. The mother, *Patient 10 Cl*, and one sister, *Patient 12 Cl*, had severe sickle-cell anemia while the second sister, *Patient 11 Cl*, showed only the sickle-cell trait. The father was non-anemic and failed to show the sickling trait. His H-S and U-L ratios were both abnormal, however, his lower body segment being seven and one-half inches greater than the upper dimension. The mother, also eunuchoid, had pulmonary tuberculosis, while the younger daughter had not matured at the age of 15 and the elder daughter, 20 years of age, had infantile sex development. A third non-anemic daughter of 17 years was normal staturally. The basal rate of the eunuchoid brother ranged from minus 26 to minus 36. His genitalia were well developed and there was potentia and libido.

The second family consisted of a mother, a son, *Patient 19 Ro*, and a daughter, *Patient 18 Wi*. Both children had severe anemia of the sickle-cell type but the mother showed only the sickling trait with a normal body configuration. The brother and sister are almost identical in stature when viewed photographically as they appear in figure 4. The span of the female is four and one-half inches in excess of her height and her U-L ratio was extremely abnormal with a disparity of eight and one-half inches. The

FIG. 2. Eunuchoid gigantism associated with familial sickle-cell anemia and familial eunuchoidism: age, 17; height, 76 in.; weight, 175 lbs.; span, 83¼ in.; upper, 33½ in.; lower, 42¾ in.

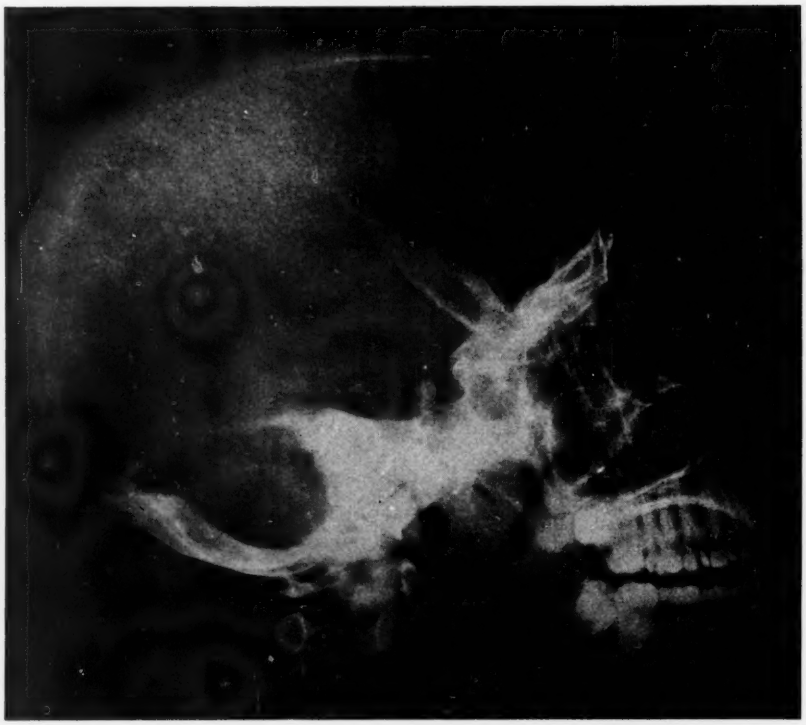

FIG. 3. Skull in sickle-cell anemia demonstrating extreme osteoporosis.

TABLE 1. STATURAL MEASUREMENTS OF 32 PATIENTS MANIFESTING SICKLE-CELL ANEMIA OR THE SICKLING TRAIT

Pt. No.	Stature	Age	Sex	Wt.	Ht.	Span	Head	Chest	Waist	Upper	Lower	Sickle Cell Anemia or Trait	Reproductive Development	Remarks
1 In	Eunuchoid	18	Female	155	64	67	23½	38	—	31	33	S. C. A.	Normal	Pregnancy 1
2 Ma	Eunuchoid	17	Female	126	61	63	22½	33	29	30	31	S. C. A.	Normal	
3 Ma	Eunuchoid	14	Female	126	64	65	22	32	33	29	35	S. C. A.	Menarche 13	—
4 Ke	Eunuchoid	24	Female	115	64	66	22	—	30	28	36	S. C. A.	Menorrhagia	
5 La	Retarded	14	Male	75	54	56	20	29	27	26	28	S. C. A.	Normal	11 yrs. stature
6 Ad	Eunuchoid	16	Male	—	61	61	21	28	—	28	33	S. C. A.	Juvenile	
7 Ad	Eunuchoid	11	Female	63	55	55	21	25	24	24	31	Negative	No Sec. Sex.	Anemia present
8 Ad.	Eunuchoid	10	Female	—	60	63	21½	30	26½	27	33	S. C. A.	No Sec. Sex.	
9 St	Eunuchoid	13	Female	82	61	62	20½	—	24	29	32	S. C. A.	Normal	
10 Cl	Eunuchoid	38	Female	116	69	—	21½	—	—	30	39	S. C. A.	Normal	
11 Cl	Eunuchoid	20	Female	156	71	77	22	31	—	31	40	Trait	Normal	
12 Cl	Eunuchoid	15	Female	86	64	64	22	—	30	29	35	S. C. A.	Juvenile	Pul. tbc.
13 Cl	Eunuchoid	17	Male	176	76	83	23	36	31	33½	42½	S. C. A.	Normal	B. M. R. −26
14 Co	Normal	25	Female	120	64	70	21½	32	30	32	32	S. C. A.	Normal	Pregnant
15 Ro	Eunuchoid	15	Female	136	63	66	22	34½	31	29	34	S. C. A.	Normal	
16 Ra	Eunuchoid	18	Female	112	65½	67	—	—	—	25	40½	S. C. A.	Normal	
17 Bu	Eunuchoid	18	Female	117	65	65	21	32	26	30	35	S. C. A.	Normal	
18 Wi	Eunuchoid	24	Female	102	62½	67	21½	29½	26	27	35½	S. C. A.	Normal	
19 Ro	Eunuchoid	33	Male	103	71½	72¾	21½	30¾	27¾	29¾	41½	S. C. A.	Small	
20 Ha	Eunuchoid	15	Male	—	59	62	20	27	25	27	32	S. C. A.	Small	
21 Sm	Eunuchoid	21	Male	125	69	71	21	33	39	31	38	S. C. A.	Small	
22 My	Eunuchoid	20	Female	114	61	—	22	35	30	27	34	S. C. A.	No Data	
23 Bl	Normal	16	Male	94	63	64	21	—	27	31	32	S. C. A.	Small	
24 Ho	Eunuchoid	13	Male	75	59	61	20½	27	27	26½	32½	S. C. A.	Small	Splenectomy
25 Fo	Eunuchoid	18	Male	114	70	73	22	33	27	33½	36½	S. C. A.	Small	
26 Wh	Normal	10	Male	60	50	50	20	25	24	24	26	S. C. A.	Normal	Chr. Toxemia
27 Be	Eunuchoid	17	Female	89	64	69	21½	29½	24½	28	36	S. C. A.	Retarded	Epiphyses Closed
28 Do	Normal	42	Male	175	71	74	22½	38	39	34½	36½	S. C. A.	Normal	
29 Wi	Eunuchoid	25	Female	131	63	64	22	23½	30	26½	36½	S. C. A.	Normal	P. I. D.
30 Hi	Eunuchoid	34	Male	137	69	72	23	35	30	31½	37½	S. C. A.	Normal	
31 Al	Normal	6	Male	42	45	46	20	23½	21	22	23	S. C. A.	Normal	
32 Gi	Eunuchoid	32	Female	110	59	65	20½	35	—	28	31	S. C. A.	Normal	

brother showed only an exaggeration of the lower segment with the characteristic slender hands and feet. Underweight was common to both, also, their weights when photographed being 102 and 103 pounds, respectively.

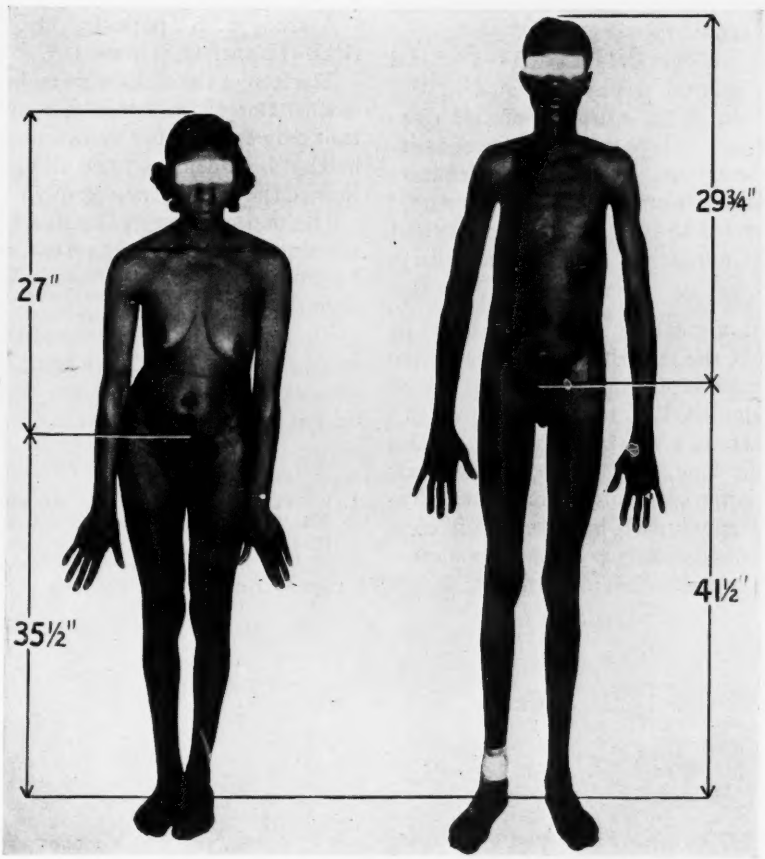

FIG. 4. Similarity of eunuchoid configuration of adult brother and sister both of whom had sickle-cell anemia. Female: age, 24; weight, 102 lbs.; span, 67 in. Male: age, 31; weight, 103 lbs.; span, 72¾ in.

A sister of *Patient 4 Ke* was found to have sickle cell anemia and slight body asymmetry. *Patients 6 Ad, 7 Ad* and *8 Ad* were brother and two sisters who showed abnormal body configuration of the eunuchoid type, although their mother was normal hemopoietically and staturally.

The mothers of each of *Patients 5 La, 23 Bi* and *24 Ho* were found to be normal as was the mother of *Patient 1 In*.

GENERAL CONSIDERATIONS

Engelbach (2) emphasizes the classical eunuchoid habitus of adolescence as showing a striking disproportion between the H-S and the U-L dimensions. Long, tapering fingers, slender feet, sparse hair growth except on the head, and marked sex underdevelopment for the age are also characteristic. Further, underweight is common, dentition is abnormal and delayed osseous union of more than one year is the rule.

Since this report is concerned only with the statural deviations found in a series of subjects having either the sickling trait or sickle-cell anemia, the measurements given in table 1 and discussed above indicate that a eunuchoid

habitus is a dominant characteristic.

Further, both the statural and hemopoietic traits may be manifested by either sex in several members of a family. While eunuchoid gigantism was found but once in our experience it is noteworthy that both parents of the subject showed a definite eunuchoid habitus and were above the average in height.

No roentgenologic data have been offered relating to delayed epiphyseal union in this group to confirm the existence of this diagnostic criterion. This pathologic state of ossification has been found so frequently in connection with sickle-cell anemia that attention need only be directed to it as having been present when sought in some of the subjects included in this report.

While not of great significance, it should be recorded that the majority of patients having sickle-cell anemia are underweight or are at the minimum level of normal body weight. Further, there is a great exaggeration in this group of the long, thin hands; slender feet; emaciated lower extremities; small facial features and subnormal head circumference. In brief, the body contour is that of undernutrition and eunuchoidism. Inasmuch as the erythrocytic sickling and the abnormal statural development are dominant familial traits it is not irrational to suggest that genetically the anterior pituitary is involved in the causation of both phenomena.

SUMMARY

A study of 32 patients, 30 of whom had sickle-cell anemia, is presented.

Thirteen of the series were male and 19 were female. One of the latter showed the sickling trait only and another was anemic but sickling had not been demonstrated although her sister showed the phenomenon readily.

The entire series of 32 subjects manifested abnormal statural development characterized by moderate to extreme degrees of eunuchoid asymmetry.

Eunuchoid habitus is proposed as a frequent accompaniment of the sickling phenomenon although no data from other sources can be offered to support the postulate.

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LETTER

CHEMICAL EQUIVALENTS

To the Editor:

I notice that the old-fashioned units of mg. per cent are still being used in the *Journal of Clinical Endocrinology* (Vol. 4, p. 275, June, 1944).

Because it is very difficult to think clearly about the chemical structure of the extracellular fluid in these terms, I should like to urge that measurements of the components of the extracellular fluid be stated in terms of chemical equivalents. As Dr. Gamble states, only in this way can their relative magnitudes and inter-relationship be clearly displayed and readily understood. The suitable term is milliequivalents per liter. This value is obtained by dividing milligrams per liter by atomic weight and multiplying by valency. Conversion to milliequivalents per liter for the individual ions is as follows:

Na^+	mg.	per 100 cc.	$\times 10 \div 23$
K^+	mg.	per 100 cc.	$\times 10 \div 39$
Ca^{++}	mg.	per 100 cc.	$\times 10 \div 40 \times 2$
Mg^{++}	mg.	per 100 cc.	$\times 10 \div 24 \times 2$
Cl^-	mg.	per 100 cc.	$\times 10 \div 35$
$HPO_4^=$	(mg. P)	per 100 cc.	$\times 10 \div 31 \times 1 \cdot 8$
$SO_4^=$	(mg. S)	per 100 cc.	$\times 10 \div 32 \times 2$

The valency of HPO_4 is taken as 1.8 because, at the normal pH of extracellular fluid, 20% of the concentration of this radical carries one equivalent of base, (BH_2PO_4), and 80% two equivalents (B_2HPO_4), B representing univalent base. Base equivalence per unit of (HPO_4) is therefore $0.2 + (0.8 \times 2) = 1.8$. The double valency sign is to this small extent inaccurate.[1]

Again as Dr. Gamble states, for the concentrations of carbonic acid ($H \cdot HCO_3$) and of bicarbonate ($B \cdot HCO_3$) convention prescribes the cumbersome statements: volume per cent CO_2 as carbonic acid and volume per cent CO_2 as bicarbonate. These volume per cent values are converted to milliequivalents per liter by dividing by 2.22.

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Massachusetts General Hospital
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August 26, 1944

[1] Chemical Anatomy, Physiology and Pathology of Extracellular Fluid: A Lecture Syllabus by J. L. Gamble, Department of Pediatrics, Harvard Medical School. (Printed by Spaulding-Moss Co., 42 Franklin Street, Boston, Massachusetts.)

Abstracts of
CURRENT ENDOCRINE LITERATURE

Editor: D. A. McGINTY. *Collaborators:* ISRAEL BRAM, RUCKER CLEVELAND, JOHN W. EVERETT, ANNA FORBES, ROBERT B. GREENBLATT, E. C. HAMBLEN, CHARLES W. HOOKER, R. G. HOSKINS, THOMAS H. MCGAVACK, A. E. MEYER, DORIS PHELPS, J. P. PRATT, E. C. REIFENSTEIN, JR., PATRICIA H. SMITH, RUTH ST. JOHN, CHARLES W. TURNER, AND HAROLD WOOSTER.

ENDOCRINE GENERAL

STRAUSS, ALFRED A., AND ERNEST H. WATSON

Studies in hormone therapy. I. The evaluation of growth hormone treatment. *J. Pediat.*, 23: 421–429. 1943.

Three methods of demonstrating growth increments are presented and an attempt is made to clarify terms and methods of measurement and statistical evaluation of growth rather than to evaluate the effectiveness of pituitary growth hormone therapy. However, 3 cases are presented (children of 8, 9, and 10 years of age) which show that height curves became convergent while the subjects were on growth hormone therapy but that the same curve tended to be divergent before and after such therapy.—*Courtesy Child Development Abstracts.*

GONADS

DANZIGER, L.

Specific treatment of psychosis due to estrogen deficiency. *Arch. Neur. & Psychiat.*, 51: 462. 1944.

The results of estrogen treatment of two groups of "involutional melancholia" patients are analyzed and contrasted. The first group were somewhat random selections in whom the onset of the psychosis was not definitely related to evidences of ovarian deficiency. The outcome of estrogen treatment was not greatly better than statistical expectancy irrespective of such treatment. Results were not any better with high-dosage than with low-dosage treatment. In a second group in which the psychosis took onset coincident with or shortly following symptoms of a disturbed climacteric the results were notably better. They varied from 61% marked improvement with lower dosages to 100% favorable results from high dosages. It is concluded that "involutional melancholia" includes many cases of true hypogonadal deficiency in which specific treatment is capable of giving notably excellent results.—*R.G.H.*

DANZIGER, L., H. T. SCHROEDER AND A. A. UNGER

Androgen therapy for involutional melancholia. *Arch. Neur. & Psychiat.*, 51: 457. 1944.

A review of the literature in English on androgen therapy of involutional melancholia in the male indicates that the incidence of prompt recovery for the treated patients is significantly higher than the incidence of prompt spontaneous recovery for control patients. Of 9 new patients treated with androgen, 5 recovered and 1 improved notably. It is calculated from 1933 U. S. Census data that the results secured were more than three times as favorable as the expected rate of spontaneous recovery.—*R.G.H.*

DOCKERTY, M. B., AND J. C. MASSON

Ovarian fibromas: a clinical and pathologic study of two hundred and eighty-three cases. *Am. J. Obst. and Gynec.*, 47: 741. 1944.

Ovarian fibromas account for 5 per cent of all ovarian tumors removed at the Mayo Clinic. The fibromas were not enountered before the age of puberty and this was taken to indicate an origin based on a desmoplastic reaction to the hemorrhage of ovulation or ovarian endometriosis. No specific diagnostic symptoms were found. Abdominal ascites occurred in 51 patients and hydrothorax in 2 patients. The authors believe the ascites was on the basis of weeping edema of the tumor due to partial obstruction of venous return. The tumors appear to arise from the spindle-cells of the ovarian cortex. An addendum gives a case report of a patient presenting a typical Meigs' syndrome.—*E.C.H.*

HARDING, FLOYD E.

Treatment of cryptorchidism. Report on treatment in thirty-eight cases with chorionic and pituitary gonadotropin and testosterone. *J. Pediat.*, 23: 451–462. 1943.

Hormonal therapy was successful in 76 per cent of the 47 patients treated by the author for cryptorchidism without mechanical obstruction.

Obstructions could be diagnosed early by endocrine treatment. The author advises surgical treatment not later than the prepubertal period in such cases in order to prevent atrophy of the undescended testicle during puberty. Under certain mental and physical conditions treatment is advised at an earlier age.—*Courtesy Child Development Abstracts.*

KLEIN, W., AND B. NEWMAN

Oral administration of diethylstilbestrol for prostatism. A clinical evaluation. *Arch. Surg.*, 48: 381. 1944.

Twenty-five patients with prostatism were treated by oral administration of diethylstilbestrol. The majority showed distinct improvement. In 71% of the cases there was a reduction in the number of nocturnal urinations by at least 50% and all except one of the patients showed some improvement of this symptom. The shrinkage of the prostate resulting from the treatment remained for at least six months. Complications consisting of enlargement of the mammary glands (most frequent) or gastric disturbances occurred in 25% of the patients. None was severe enough to cause disability and all cleared up soon after medication was discontinued. The necessity of treating each patient individually and of regulating the dose by close observation of his progress was emphasized. It was pointed out that, in general, favorable results may be expected in a person who is well preserved for his age and mentally alert and whose prostate is of the general hyperplastic type (senile hypertrophy), while in one who is suffering from advanced arteriosclerosis or whose urinary obstruction is due to fibrous bars and sclerosis of the wall of the bladder, good results cannot be expected.—*D.P.*

KRICHESKY, B., J. A. BENJAMIN AND C. SLATER

Inactivation of endogenous androgens by the liver in rabbits. *Endocrinol.*, 32: 345. 1943.

Whole testes of the rabbit were transplanted intramesenterically with minimal trauma or disturbance to their normal circulation. After establishment of vascular anastomosis with mesenteric circulation, the original circulation via the spermatic arteries and veins was severed, resulting in venous drainage only through the portal circulation. Passage of endogenous androgens through the portal system and the liver failed to maintain prostatic implants. A later secondary vascular anastomosis to the body wall stimulated growth of the prostatic implants and restored their normal histologic structure. Evidence was obtained indicating that only a portion of the total androgen production by the testes was sufficient to maintain transplanted prostatic tissue.—*Author's Summary.*

MILLER, H. C.

Effect of the injection of sex hormones on serum and muscle electrolyte of rats. *Endocrinol.*, 32: 443. 1943.

Concentrations of potassium were found to be abnormally low in the muscle of rats injected with estradiol benzoate and testosterone propionate over a period of several months. On the basis of their effectiveness in decreasing the concentration of potassium in the muscle, progesterone, estradiol and testosterone may be ranked in descending order.—*Author's Summary.*

NATION, E. F., H. A. EDMONDSON AND R. W. HAMMACK

Interstitial cell tumors of the testis. Report of three new cases. *Arch. Surg.*, 48: 415. 1944.

Twenty-six acceptable interstitial cell tumors of the testis have been reported to date, including 3 new ones reported here. Of this number, 21 were benign and 5 malignant. One of the 3 reported here was malignant and occurred in an 82-year-old man. The other 2 were in patients aged 30 and 34 years. One of the patients had gynecomastia which failed to regress after orchidectomy was performed. Each of the 6 children in whom tumors occurred had precocious bodily and sexual development. Three (15%) of the adults had gynecomastia. Interstitial cell tumors of the testis are usually nodular and yellow or yellow-brown. The microscopic picture is characteristic; there are well circumscribed groups of liver-like cells with rather small, round nuclei and many punctate nucleoli, some of which are eccentric. It is believed that the manifestations of these tumors offer further proof that the interstitial cells of the testis are the primary source of androgen. —*Author's Summary.*

PLAUT, A., AND S. STANDARD

Cystomyoma of seminal vesicle. *Ann. Surg.*, 119: 253. 1944.

The case of a sixty-six-year old man in whom was found a large myomatous tumor attached to the ampulla or seminal vesicle is reported. The tumor closely resembled uterine myoma. A full description is given, together with physical and

laboratory findings. Only four similar cases have been reported, one of them in a living patient. These are reviewed. Remnants of the midportion of the Mullerian duct are said to be the source of these tumors.—*D.P.*

SALEEBY, E. R.

Teratoma of the testicle. Metastasis to the epigastrium treated by bilateral orchidectomy—recovery. *Ann. Surg.*, 119: 262. 1944.

A case is reported of a patient who had a teratoma of the left testicle, with a large metastatic retroperitoneal mass. He was treated by bilateral orchidectomy, with roentgenotherapy to reduce the epigastric mass. Prior to operation the Friedman test was positive, qualitative serum gonadotrophins were well within the range of pregnancy and the urine estrogens and 17-ketosteroids were normal. Six weeks postoperatively, the Friedman test was negative, the quantitative serum gonadotrophins nondemonstrable, the quantitative urine gonadotrophins slightly above the normal range. Subsequently, the gonadotrophic titer of the urine returned to normal. The operation was followed by a steady improvement in the patient's general physical condition and 14 months later he was enjoying the best of health. At this time, a physical examination, including hormone assays and roentgenologic studies, revealed no evidence of tumor recurrence. It was suggested that, while it is not known what relation there is between sex hormone and cancer, there is, apparently, some carcinogenic agent which must have been influenced by the removal of the testis.—*D.P.*

PANCREAS

CARRASCO-FORMIGUERA, R.

Alloxan diabetes in dogs. *J. Lab. & Clin. Med.*, 29: 510. 1944.

Five dogs were injected with alloxan in amounts varying from 100 to 300 mgm. per kg. One animal that received 300 mgm. per kg. intravenously in a single injection died within 25 minutes, and a second, within 20 hours from three divided doses totalling 300 mgm. per kg. The remaining dogs lived several days or more, and developed diabetes mellitus. This was transient in one as it disappeared spontaneously within 10 days. The degree of pancreatic damage and the severity of the diabetes showed no correlation. Indeed, in one animal that developed a diabetes of great severity, biopsy of the pancreas failed to reveal any histologic changes whatsoever. In all three dogs, diabetes with hyperglycemia and glycosuria was well established within 24 hours. The changes in these dogs differed in several respects from those seen in rabbits made diabetic by alloxan. The initial hyperglycemia began later, lasted longer, and was followed by a less severe fall in the blood sugar which never reached hypoglycemic levels. Toxic reactions not related to the variations in blood sugar were described; here were included emesis, depression, paresis, and stupor. Even when a lethargic state was present with hypoglycemia, the author found intravenously administered glucose an effective therapeutic agent.—*T.H.McG.*

PRIESTLY, J. T., M. W. COMFORT, and J. RADCLIFFE, JR.

Total pancreatectomy for hyperinsulinism due to an islet-cell adenoma; survival and cure at sixteen months after operation. Presentation of metabolic studies. *Ann. Surg.*, 119: 211. 1944.

A case of hypoglycemia due to hyperinsulinism from a small adenoma of the islets of Langerhans in which a total one-stage pancreatectomy was performed is reported herewith. A less radical procedure would have failed to cure the patient, since the adenoma was located in the head of the gland, in intimate proximity to the duodenum. This is believed to be the first case in history of total pancreatectomy for benign or malignant disease in which the patient has survived beyond the immediate postoperative period. Total pancreatectomy was followed by a relatively mild degree of diabetes. Disturbance of carbohydrate digestion was not detected by the methods used, while digestion of protein and fat was definitely diminished. About thirty-five to seventy per cent of ingested fat and twenty-five to fifty-five per cent of ingested nitrogen could be accounted for in the feces. A positive nitrogen balance occurred in spite of the large loss of nitrogen in the feces. Foodstuffs in the urine and feces accounted for twenty-one to thirty-four per cent of the calories ingested. The percentage of total fat in the stools as neutral fat varied from fifty-four to sixty-nine per cent. The dried weight of the stools was greater than values obtained for healthy persons. The patient has remained in excellent health, sixteen months after operation. Evidence of deficiency of lipocaic has not developed.—*Author's Summary.*

PARATHYROID

BROUGHER, J. C.

Parathyroid extract in preeclamptic toxemia. *Northwest. Med.*, 43: 198, 1944.

Summarizes results of treatment of over 1800 cases of early preeclamptic toxemias including 1000 cases previously reported. Parathyroid extract was found useful in relieving edema and in lowering the blood pressure in mild preeclamptic toxemia.—*D.A.M.*

THYROID

BATEMAN, J. FREMONT

Schizophrenic reaction-types simulating thyroid disease. *Ohio State M. J.*, 39: 421. 1943.

Because of the outward similarity of hyperthyroidism and sympathicotonic states, the author has attempted to show that this apparent similarity is parasympathetic activity, and that so often symptoms of cranial autonomic inhibition are misinterpreted as thyroid disease. The schizophrenic reaction type simulates schizophrenia during the acute illness but differs in mode of onset, time of life and the absence of prepsychotic evidence of schizoidism. This group shows profound evidence of cranial autonomic inhibition. These findings are interpreted by some surgeons as evidence of hyperthyroidism even though there is no evidence of glandular enlargement. This study of 128 patients over a period of 14 years suggests that a more careful analysis be made of the secondary neurogenic symptoms found in schizophrenia and thyroid disease. The term nervousness is more generally associated with psychogenic disease. The thyroid surgeon too often interprets nervousness in terms of secondary neurogenic disease. Emotional instability should be interpreted in terms of the effect in order properly to evaluate metabolic influences. When there is direct evidence of psychic trauma or of psychopathic trait the practice of thyroidectomy leaves untouched the fundamental disorder. This paper demonstrates the need for more careful consultation between the surgeon and the psychiatrist.—*Author's Abstract.*

CLAY, R. C., AND S. S. BLACKMAN, JR.

Lateral aberrant thyroid: metastasis to the lymph nodes from primary carcinoma of the thyroid gland. *Arch. Surg.*, 48: 223. 1944.

Two cases of the condition long referred to in the literature as "lateral aberrant cervical thyroid" were studied. In both cases the lateral masses proved to be metastases in lymph nodes, while the primary tumor in each case was found in the homolateral lobe of the thyroid gland. The pertinent literature was reviewed and the conclusion drawn that the lesion known as lateral aberrant cervical thyroid should be interpreted, until satisfactory evidence to the contrary is adduced, as tumor metastases in the cervical lymph nodes from small primary carcinomas in the homolateral lobe of the thyroid. It was pointed out that the microscopic appearance of these tumors is not a good index of malignancy since metastases develop which look histologically "benign." It was suggested that, when such a lesion is found in the lateral cervical region, the thyroid should be explored, at least the homolateral lobe removed and the patient watched for the subsequent appearance of lesions in the opposite lobe.—*D.P.*

DRILL, V. A., R. OVERMAN AND J. H. LEATHEM

Relation of the B vitamins to ovarian function during experimental hyperthyroidism. *Endocrinol.*, 32: 327. 1943.

Hyperthyroid rats, receiving a synthetic diet and a small yeast supplement, rapidly lost weight when 100 mg. of thyroid gland was fed each day. The food intake remained essentially the same as that of the control rats. After 10 to 17 days of thyroid feeding all of these rats had entered continuous diestrus. By administering sufficient B vitamins to two groups of hyperthyroid rats the food intake was increased, the loss of weight was prevented and a slight gain in weight obtained, while normal estrous cycles were maintained throughout the 79 days of thyroid feeding. The ovaries and the pituitary of the hyperthyroid rats receiving the small yeast supplement showed a loss of weight. The histologic picture of these ovaries suggested insufficient gonadotropic hormone secretion. The hyperthyroid rats receiving the high B vitamin diet maintained normal ovarian and pituitary weight, and showed a normal ovarian histology.—*Author's Summary.*

FRANTZ, V. K., R. P. BALL, A. S. KESTON AND W. W. PALMER

Thyroid carcinoma with metastases: studied with radioactive iodine. *Ann. Surg.*, 119: 668. 1944.

This is a report of a case thought to be the

first in which the function of metastases from thyroid carcinoma has been studied by means of radio-iodine storage. Only one metastasis consistently showed appreciable uptake of the material. At autopsy, the bulk of the metastatic tissue was undifferentiated. The metastasis which showed consistent uptake of iodine was the only one which grossly resembled thyroid tissue, and which, microscopically, showed chiefly well differentiated tumor. The authors believed that the two types of tumor were present in this patient before the administration of the radio-iodine, since, from the outset, there was no uptake in most of the lesions with tracer doses. The rarity of occurrence of anaplastic changes in thyroid carcinoma of the adenoma malignum type was pointed out. There was no clinical evidence that the radio-activity of the iodine was effective, in the amounts given, in therapeutic "internal irradiation." However, in view of the fact that some well differentiated tumors of the thyroid are capable of storing iodine, it was suggested that effective therapeutic internal irradiation of metastases may be achieved with large enough doses of radioactive iodine in selected cases, possibly where the amount of tumor tissue is small. It was emphasized that tracer doses of iodine may be valuable diagnostically, but only if there is localization. Failure of uptake does not mean that the tumor in question is not of thyroid origin.—*D.P.*

HAIK, MAJOR G. M.

Progressive exophthalmos in toxic disease of the thyroid gland. A review of the recent literature, with the report of a case of progressive postthyroidectomy proptosis in a six-year old negro girl. *Arch. Surg.*, 48: 214. 1944.

The treatment of exophthalmos associated with hyperthyroidism, particularly of the variety which becomes progressive after thyroidectomy, has hitherto been unsatisfactory. Thyroidectomy, far from correcting the condition, frequently seems to aggravate it. Recent studies indicate that the cause of exophthalmos in hyperthyroidism is local edema, sometimes associated with hypertrophy of the extraocular muscles. The proposal that irradiation be substituted for thyroidectomy is based on the theory that with a less abrupt alteration in the endocrine balance there is a greater chance for more gradual readjustment of the optic structures. A case of progressive postthyroidectomy exophthalmos is reported and is analyzed in the light of these new concepts. It is unusual because of the extreme youth and the race (Negro) of the patient.—*Author's Summary.*

HAMILTON, JOSEPH G., MAYO H. SOLEY, WILLIAM A. REILLY AND KARL B. EICHORN

Radioactive iodine studies in childhood hypothyroidism. *Am. J. Dis. Child.*, 66: 495–502. 1943.

Radioactive iodine was administered orally to 10 children with severe hypothyroidism. It was found that the thyroids of children with hypothyroidism and without goiters were able to concentrate only small amounts of orally administered iodine as compared with those of normal children or adults.—*Courtesy Child Development Abstracts.*

HELLWIG, C. A.

The goiter heart. An experimental study *Arch. Surg.*, 48: 27. 1944.

Goiters were produced in twenty-one white rats by feeding the goitrogenic diet of Wegelin. Eleven of the experimental animals drank pure well water during the experimental period, while the remaining animals were given a one per cent solution of calcium chloride as drinking water. Anatomic findings at the end of the experimental period were compared with the findings in nine control rats. The hearts of the goitrous animals showed no histologic changes which would suggest a direct toxic effect of goiter on the myocardium. Lymphocytic infiltration, degeneration of muscle fibers and scar formation were common in the hearts of the experimental animals but these changes were encountered just as often in the hearts of the non-goitrous controls. It was suggested that they must be explained, therefore, by causes which were active in all three groups, possibly some intercurrent infection. The only positive anatomic finding was a significant hypertrophy of the left ventricle in the rats which received the calcium-rich diet. This observation was interpreted as suggesting that left ventricular strain in endemic goiter may be due to a direct effect exerted on the heart muscle by the same factor which is responsible for the development of goiter, e.g., an excess of calcium in the food. That the experimental results are in accord with the experience of most observers that there is no anatomic type of endemic goiter which predisposes to cardiac complications was pointed out.—*D.P.*